Public Assessment Report
Mutual Recognition Procedure

Optivate 100 IU/mL, powder for solution for injection (Human coagulation Factor VIII von Willebrand factor)

Procedure No: UK/H/4591/01/E01
UK Licence No: PL 08801/0051

Bio Products Laboratory (BPL)
Lay Summary

Optivate 100 IU/mL, powder for solution for injection
(Human coagulation Factor VIII von Willebrand factor)

This is a summary of the public assessment report (PAR) for Optivate 100 IU/mL, powder for solution for injection, human coagulation Factor VIII von Willebrand factor (PL 08801/0051; UK/H/4591/01/E01). It explains how Optivate 100 IU/mL, powder for solution for injection was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Optivate 100 IU/mL, powder for solution for injection.

For practical information about using Optivate 100 IU/mL, powder for solution for injection, patients should read the patient information leaflet (PIL) or contact their doctor or pharmacist.

What is Optivate 100 IU/mL, powder for solution for injection and what is it used for?
Optivate 100 IU/mL, powder for solution for injection is a high purity factor VIII concentrate from human blood plasma obtained from screened donors. This prescription-only medicine is effective in the treatment and prevention of bleeding in patients with haemophilia A (congenital factor VIII deficiency in the blood).

How does Optivate 100 IU/mL, powder for solution for injection work?
Optivate 100 IU/mL, powder for solution for injection contains the active substance human coagulation factor VIII. Coagulation factor VIII is a blood-clotting protein which naturally circulates in the body in an inactive form bound to another molecule called von Willebrand factor. In response to bleeding, either spontaneous or due to injury to blood vessels, coagulation factor VIII separates from von Willebrand Factor setting off a chain of reactions which results in the formation of a blood clot. Patients with haemophilia A are deficient in coagulation factor VIII and therefore unable to form clots.

How is Optivate 100 IU/mL, powder for solution for injection used?
Treatment with Optivate 100 IU/mL, powder for solution for injection will be initiated under the supervision of physician experienced in the treatment of haemophilia. Optivate 100 IU/mL, powder for solution for injection is given by injection into a vein (intravenously).

Please read Section 3 of the PIL for detailed information on dosing recommendations.

What benefits of Optivate 100 IU/mL, powder for solution for injection have been shown in studies?
Several clinical studies have been performed that demonstrate that Optivate 100 IU/mL, powder for solution for injection is effective in the treatment and prevention of bleeding in patients with haemophilia A. No new safety issues were identified during these studies.

What are the possible side effects from Optivate 100 IU/mL, powder for solution for injection?
Like all medicines, Optivate 100 IU/mL, powder for solution for injection can cause side
effects, although not everybody gets them.

For information about side effects that may occur with using Optivate 100 IU/mL, powder for solution for injection, please refer to the PIL or the Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

**Why is Optivate 100 IU/mL, powder for solution for injection approved?**

Optivate 100 IU/mL, powder for solution for injection was first approved in the UK 10th December 2004. Since then it has also been granted in Cyprus, Denmark, Malta and Portugal. No new or unexpected safety concerns arose from this application seeking authorisation of Optivate 100 IU/mL, powder for solution for injection in Austria, Belgium, Czech Republic, Estonia, Hungary, Ireland, Latvia, Lithuania, The Netherlands, Poland, Romania and Slovakia. It was, therefore, considered that the benefits of Optivate 100 IU/mL, powder for solution for injection outweigh the risks and the grant of the marketing authorisation was recommended.

**What measures are being taken to ensure the safe and effective use of Optivate 100 IU/mL, powder for solution for injection?**

A risk management plan has been developed to ensure that Optivate 100 IU/mL, powder for solution for injection is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the PIL for this product, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

**Other information about Optivate 100 IU/mL, powder for solution for injection**

Austria, Belgium, Czech Republic, Estonia, Hungary, Ireland, Latvia, Lithuania, The Netherlands, Poland, Romania and Slovakia agreed to grant a marketing authorisation for Optivate 100 IU/mL, powder for solution for injection on 15 April 2015. The marketing authorisation in the UK was granted on 22 April 2015.

The full PAR for Optivate 100 IU/mL, powder for solution for injection follows this summary.

For more information about treatment with Optivate 100 IU/mL, powder for solution for injection, read the PIL or contact your doctor or pharmacist.

This summary was last updated in June 2015.
## TABLE OF CONTENTS

I  Introduction ...................................................................................................................... 5

II  Quality aspects.................................................................................................................. 6
   II.1 Introduction ..................................................................................................................... 6
   II.2 Drug substance ................................................................................................................ 6
   II.3 Drug product .................................................................................................................... 7
   II.4 Manufacture ..................................................................................................................... 9
   II.5 Control of excipients ..................................................................................................... 10
   II.6 Control of drug product ................................................................................................. 10
   II.7 Container closure system ............................................................................................... 11
   II.8 Stability .......................................................................................................................... 11
   II.9 Appendices .................................................................................................................... 11
   II.10 Assessor’s comments on the spc, labels and package leaflet ...................................... 13
   II.11 Assessor’s overall conclusions on quality and advice ................................................. 13
   II.12 Summary of product characteristics, patient information leaflet & labels ............... 13

III  Non-clinical aspects ....................................................................................................... 18
   III.1 Introduction .................................................................................................................. 18
   III.2 Pharmacology ............................................................................................................... 18
   III.3 Pharmacokinetics ......................................................................................................... 19
   III.4 Toxicology ................................................................................................................... 20
   III.5 Assessor’s overall conclusion ...................................................................................... 24

IV  Clinical aspects ............................................................................................................... 25
   IV.1 Introduction .................................................................................................................. 25
   IV.2 Clinical trials ................................................................................................................ 27
   IV.3 Clinical expert report ................................................................................................... 48
   IV.4 Product particulars ....................................................................................................... 48
   IV.5 Assessors overall comments ....................................................................................... 49
   IV.6 Recommendation ......................................................................................................... 49

V  User consultation ............................................................................................................ 49

VI  Overall conclusion, benefit/risk assessment and recommendation ............................... 49
I  Introduction

Based on the review of the data on quality, safety and efficacy, the Member States have granted a marketing authorisation (MA) to Bio Products Laboratory (BPL) for the medicinal product Optivate 100 IU/mL, powder for solution for injection. This prescription-only medicine is indicated for the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).

This application was submitted using the repeat-use Mutual Recognition Procedure (MRP), with the UK as Reference Member State (RMS) and Austria, Belgium, Czech Republic, Estonia, Hungary, Ireland, Latvia, Lithuania, The Netherlands, Poland, Romania and Slovakia as Concerned Member States (CMS). This application was made under Article 8.3 of Directive 2001/83/EC, as amended, for a known active substance.

Previous to Optivate, BPL had developed a factor VIII complex concentrate with its natural carrier protein, von Willebrand Factor (VWF) called Dried Factor VIII, Fraction, 8Y (UK PL 08801/0021) which has been in use since July 1995. The rationale for the development of Optivate was twofold: (a) to produce a high purity FVIII and VWF complex and (b) to add an extra specific antiviral step to the manufacturing process.

Haemophilia A is a sex-linked hereditary disorder of blood coagulation due to decreased levels of coagulation factor VIII and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as results of accidental or surgical trauma. Plasma levels of coagulation factor VIII are increased by replacement therapy leading to a temporary correction of the factor deficiency and correction of the bleeding tendencies.

The following clinical studies were presented in the clinical dossier: pharmacokinetic study; safety and efficacy study; surgery study; study in children; study in other surgical procedures. All data were considered to be satisfactory.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that the pharmacovigilance system, as described by the MA holder, fulfils the requirements and provides adequate evidence that the MA holder has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. The MA holder has provided a Risk Management Plan (RMP).

The MA holder has provided satisfactory justification for not providing an Environmental Risk Assessment (ERA). ERAs are not required for vaccines.

The RMS and CMSs considered that the application could be approved at the end of procedure (Day 90) on 15 April 2015. After a subsequent national phase, a licence was granted in the UK on 22 April 2015.
II Quality aspects
II.1 Introduction

REQUESTS FOR INSPECTION ACTION PRIOR TO AUTHORISATION
No action requested.

Legal status
POM.

II.1.2 Use
Optivate 100 IU/ml powder for solution for injection is a freeze-dried coagulation factor VIII and von Willebrand factor (VWF) concentrate for reconstitution in water for injection. It is to be used in haemophilia A patients for the treatment or prophylaxis of bleeding. It may also be used in the management of acquired factor VIII deficiency.

Optivate 100 IU/mL, powder for solution for injection is derived from fresh-frozen, platelet-poor plasma. When infused into a patient, factor VIII binds to von Willebrand factor in the circulation, which provides protection from proteolysis and transports FVIII to a site of bleeding. Activated factor VIII acts as a cofactor for activated factor IX, which in turn accelerates the conversion of factor X. Factor X converts prothrombin to thrombin, which then converts fibrinogen to fibrin and allows a blood clot to form.

In addition to its protection of factor VIII, VWF mediates platelet adhesion to sites of vascular injury and plays a role in platelet aggregation. Patients with von Willebrand's disease will bleed profusely, especially from mucosal surfaces and will require replacement therapy with both VWF and factor VIII.

The current product is a development of PL 08801/0021 Dried factor VIII injection, type 8Y.

II.1.3 Scientific advice
NA

II.1.4 Legal status
POM

II.2 DRUG SUBSTANCE

II.2.1 General information
The drug substance is defined as the individual plasma donations that make up the initial plasma pool from which the active ingredients FVIII and VWF are purified. The collection and control of these plasma donations is described in the BPL Plasma Master File. As such there is no drug substance section in the QOS or Module 3. This is acceptable.

II.2.2 Manufacture
The plasma used for the manufacture of Optivate 100 IU/mL, powder for solution for injection is covered by a PMF which has been recently approved.
II.2.3 Control of drug substance

**Specification**
The plasma complies with the Ph.Eur. monograph 'Human Plasma for Fractionation.' Tests for total protein and for factor VIII potency are also acceptable.

**Validation of analytical procedures**
Validation of analytical procedures has been performed and is adequate.

II.2.4 Reference standards or materials
NA.

II.2.5 Container closure system
Details of the containers used for storage of plasma have been provided. The packaging material complies with the Ph.Eur. 'Sterile plastic containers for human blood and blood components'. The MAH has confirmed that the anticoagulant used in the plasma packs would comply with USP and Ph.Eur.

II.2.6 Stability
The proposed shelf-life for plasma for use in Optivate 100 IU/mL, powder for solution for injection manufacture is based upon results from a stability review. This proposed shelf-life for plasma is acceptable.

II.3 DRUG PRODUCT

II.3.1 Description and composition of the drug product
The composition of Optivate 100 IU/mL, powder for solution for injection is shown in the table below.

<table>
<thead>
<tr>
<th>Table 1. Composition of Optivate 100 IU/mL, powder for solution for injection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ingredients</strong></td>
</tr>
<tr>
<td>Active ingredients</td>
</tr>
<tr>
<td>Von Willebrand Factor (VWF)</td>
</tr>
<tr>
<td>Inactive Ingredients</td>
</tr>
</tbody>
</table>
Optivate 100 IU/mL, powder for solution for injection is a white or pale yellow freeze-dried powder. It is available in either 250 IU, for reconstitution in 2.5 ml, 500 IU, for reconstitution in 5 ml water for injections, or 1000 IU, for reconstitution in 10 ml water for injections.

All clinical trials were carried out with the formulation proposed for marketing.

**Components of the drug product**
Optivate 100 IU/mL, powder for solution for injection contains the following excipients: sodium chloride, sodium citrate, calcium chloride, polysorbate 20 and trehalose. The reasons for their presence have been adequately described. The formulation may also contain the following contaminants, tri-n-butyl phosphate (TnBP), trometamol, glycine, heparin and 5m HCL. These are used during the manufacturing process and are later removed, although some trace amounts may remain.

**II.3.2 Formulation development**
The formulation of Optivate 100 IU/mL, powder for solution for injection was based on PL 08801/002 Dried factor VIII injection, type 8Y and the new process has been adequately described.

**Physicochemical and biological properties**
Optivate 100 IU/mL, powder for solution for injection is a concentrate enriched with FVIII and VWF. It is readily soluble in water for injections and therefore complies with the Ph.Eur. requirement that human coagulation factor VIII dissolves within 10 minutes.

The applicant has provided an analysis of the protein composition in pilot-scale batches and manufacturing-scale batches that were produced to date for clinical trials. These were acceptable.
**Von Willebrand factor in Optivate**
The applicant has carried out considerable characterisation studies on VWF in Optivate 100 IU/mL, powder for solution for injection and has provided adequate details of FVIII monitored throughout the process which is satisfactory.

**Overages**
There is no overage in this formulation.

**Manufacturing process development**
The manufacture of Optivate 100 IU/mL, powder for solution for injection is similar to the Dried Factor VIII, Fraction, 8Y process. The applicant has included an extra viral inactivation step, in addition to heat treatment, in the manufacturing process.

The manufacturing process development has been adequately described and is satisfactory.

**Microbiological attributes**
The applicant cites several factors that will help to decrease the bioburden in the product. Two specific viral inactivation steps are included in the method but further steps also significantly decrease bioburden. The product is adequately sterilised and the final product is tested for sterility and pyrogenicity. Closure integrity studies have demonstrated that the final container is suitable. The applicant has also carried out viral validation studies, see below.

**Compatibility**
The applicant carried out adequate stability studies to determine the stability of the reconstituted solution in the appropriate containers and closures, however further studies are required to support the defined stability time period.

These studies are discussed further in the stability section.

**II.4 Manufacture**

**II.4.1 Manufacturer**
The applicant has provided all details of manufacturers responsible for the manufacture and batch release of Optivate 100 IU/mL, powder for solution for injection and the necessary manufacturers licences.

**II.4.2 Batch formula**
Batch formulae have been provided for each licensed scale of manufacture and are satisfactory. The MAH confirms that should the finished product test positive for viral markers then that batch would not be released and any other intermediates/products manufactured from the same pools involved would also be held pending investigation. This is satisfactory.

**II.4.3 Description of manufacturing process and process controls**
The applicant has provided a flow chart and detailed description of the manufacturing process. Details of the in-process controls are also provided in both tabular and text format. This is acceptable.
II.4.4 Control of critical steps and intermediates  
These have been adequately described and are satisfactory.

II.4.5 Process validation and/or evaluation  
The applicant has provided batch analysis data from several finished product batches and extensive data for process validation. The applicant has provided manufacturing records and batch histories for several full-scale batches which adequately demonstrate that the manufacturing process is consistent and well controlled. The product is well characterised throughout the process.

II.5 Control of excipients

II.5.1 Specifications  
Most excipients and ingredients used in the manufacture of Optivate 100 IU/mL, powder for solution for injection are Ph.Eur. grade. Specifications for those that are not have been provided in the dossier.

Ph.Eur. materials will be routinely tested and control testing will be performed on excipients of biological origin or those that are bland enough to support bacterial growth. Other excipients will be tested for microbial control periodically.

The applicant proposes to use some non-Ph.Eur. tests to examine excipients. The applicant has provided a comparison of their proposed non-pharmacopoeial methods and limits for excipients to the standard Ph.Eur. methods. These alternative tests were comparable and so their use is acceptable.

II.5.2 Excipients of human or animal origin  
Excipients of animal origin are adequately controlled.

II.6 Control of drug product

II.6.1 Specification  
The finished product specification has been provided and is satisfactory.

II.6.2 Analytical procedures  
Methods are provided for all analytical procedures. The applicant has validated the methods and provided a summary of the validation results. These are satisfactory.

II.6.3 Batch analyses  
The applicant has provided batch analysis data for several batches of Optivate 100 IU/mL, powder for solution for injection which support a 36 month shelf life.

II.6.4 Characterisation of impurities  
The applicant has provided a list of the impurities in Optivate 100 IU/mL, powder for solution for injection and has set limits for all these impurities in the finished product specification. This is satisfactory.
II.6.5 Justification of specification
The specifications have been adequately justified and reflect the batch analysis data supplied in the dossier.

II.6.6 Reference standards or materials
The reference standards used for FVIII and VWF have been adequately described and are satisfactory.

II.7 Container closure system
The finished product is presented as a freeze-dried powder within a 10 mL (250 IU and 500 IU) or 30 mL (1000 IU) Ph.Eur. type 1, neutral borosilicate glass vials, with a halobutyl stopper and tamper-evident seal. The vials are packaged in an outer carton to protect the product from light. Stability studies have been carried out with the product packaged in clear, neutral glass vials. This is satisfactory.

Optivate 100 IU/mL, powder for solution for injection is supplied with a glass vial of sterilised WFI, Ph.Eur., of appropriate volume for reconstitution of the freeze-dried plug. The details for the sterilised WFI have been supplied.

A needle-less transfer device (Mix2Vial) used for reconstitution is supplied for each vial of product. An administration kit may be supplied separately on request. This consists of alcohol swabs, a sterile butterfly no. 23 needle for administration of the product, a 20 mL syringe and plaster.

II.8 Stability

Finished product
BPL has presented data from several batches which provide sufficient evidence to support the applicants claimed shelf-life.

The process control and storage of intermediates have also been adequately described and are satisfactory. The applicant has also adequately tested the stability of the product after reconstitution.

Compatibility with reconstitution components

Stoppers
The applicant then provided additional data to test compatibility with stoppers for several batches of Optivate 100 IU/mL, powder for solution for injection. The results were satisfactory.

Mix2Vial device
The applicant has studied the stability of the reconstituted solution after storage in the Mix2Vial for a defined time-period. The results were satisfactory.

The applicant has provided confirmation that the device is CE marked and has been evaluated for suitability according to Medical Devices Directive 93/42/EEC. It is subject to an
appropriate sterilisation procedure and is designated as single use and has been assigned an appropriate shelf-life when stored within the Optivate product outer carton.

 suitability for the intended use and compatibility with Optivate product
Compatibility of Optivate 100 IU/mL, powder for solution for injection with the Mix2Vial device and stability after reconstitution has been studied and found to be acceptable. It is accepted that no components present are expected to lead to additional leaching and additional studies are not required in addition to the overall compatibility testing of the reconstituted product.

A study was presented to demonstrate comparability of the proposed device with the current reconstitution procedure and equipment. The study adequately demonstrated that the proposed device has no negative impact on product quality.

II.8.1 Stability summary and conclusion
The applicant has proposed a shelf life of 36 months at 25°C. This is acceptable.

II.8.2 Post-approval stability protocol and stability commitment
The applicant will routinely enter batches of licensed products onto stability and will continue to provide updates on the stability of Optivate 100 IU/mL, powder for solution for injection to demonstrate compliance with the proposed shelf life.

II.9 APPENDICES

II.9.1 Facilities and equipment
Not applicable

II.9.2 Adventitious agents safety evaluation
Non-viral adventitious agents
The applicant follows GMP procedures to control the entry of microorganisms into the processing areas and monitor their presence. All biological raw materials, and all materials that are bland enough to support bacterial growth, are tested for TVAC. The utilities undergo regular microbial testing and clean rooms are monitored. Intermediates in the production process are tested for TVAC. The finished product is tested for sterility and pyrogenicity.

Plasma is sourced from the USA, to minimise the risk of transmission of TSE agents. Heparin is from an animal source not considered to be at risk of TSE.

Viral adventitious agents
The applicant considers that there are several factors in the Optivate 100 IU/mL, powder for solution for injection production process that contribute to its viral safety. These have been adequately described and are satisfactory.

Viral validation studies
Viral validation studies were carried out adequately and the virus reduction factors in Optivate 100 IU/mL, powder for solution for injection satisfactorily described. Inactivation of the defined viruses was demonstrated.
II.9.3 Novel excipients
Not applicable.

II.10 ASSESSOR’S COMMENTS ON THE SPC, LABELS AND PACKAGE LEAFLET

The relevant sections of the SPC have been checked and comply with the SPC guideline.

Comment on expert report
The pharmaceutical expert report is satisfactory.

II.11 ASSESSOR’s OVERALL CONCLUSIONS ON QUALITY AND ADVICE

This application may be approved.

II.12 Summary of Product Characteristics, Patient Information Leaflet & Labels

Current versions of the SmPC and PIL are available on the MHRA website via the following link. Please search for the SPC and PIL for the medicinal product you require.
http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs/index.htm

The current labelling is provided below:
Optivate 100 IU/mL powder for solution for injection

Optivate®
Powder and solvent for solution for injection
Human coagulation factor VIII

• FOR INTRAVENOUS USE ONLY.

Sterilised water for injections

For intravenous use only.

Sterilised water for injections

For intravenous use only.

Sterilised water for injections

For intravenous use only.
III Non-clinical aspects

III.1 Introduction

Optivate 100 IU/ml powder for solution for injection is a human coagulation factor VIII (FVIII)/Von Willebrand Factor (VWF) complex. The proposed therapeutic indications (from the SmPC) are: “Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital FVIII deficiency). This product may be used in the management of acquired FVIII deficiency”.

This is a national application under Article 8.3(i) for a known active substance. Whilst Optivate 100 IU/ml powder for solution for injection is considered to be a new product, it has been developed from an existing marketed Dried Factor VIII, Fraction, 8Y (PL 08801/0021).

Optivate 100 IU/ml powder for solution for injection is presented as a lyophilised powder for intravenous (i.v.) injection containing nominally 250 IU, 500 IU or 1000 IU FVIII per vial. The VWF is the natural stabiliser for FVIII in the circulation and is the only protein stabiliser present in Optivate 100 IU/ml powder for solution for injection. The dosage to be recommended is between 17 and 30 IU/kg representing a dose of 1190–2100 IU/patient (assuming 70 kg bw). For prophylaxis of bleeding the recommended dosage is 20–40 IU/kg bw three times per week representing 4200–8400 IU/patient/week. Individual bleeds are treated as required but prophylactic treatment may be on a regular basis.

The factors which have limited the non-clinical testing programme are that human FVIII will probably be immunogenic in test animals and the availability of animals deficient in its production is limited. Also, there is extensive clinical experience with the current FVIII BPL product, Dried Factor VIII, Fraction, 8Y (PL 08801/0021), which has been marketed for over 15 years and over 300 million IU of Dried Factor VIII, Fraction, 8Y have been distributed (in the UK alone). The essential differences between the Optivate 100 IU/ml powder for solution for injection and Dried Factor VIII, Fraction, 8Y formulations are that Optivate 100 IU/ml powder for solution for injection contains polysorbate 20 and trehalose in the place of sucrose in Dried Factor VIII, Fraction, 8Y. Polysorbate 20 has been included to improve the solubility of the highly concentrated FVIII/VWF and trehalose to preserve the solubility of the product after freeze-drying and terminal heat treatment. Therefore, the pre-clinical safety assessment focused on the toxicology of the excipients new to the formulation.

III.1.1 GLP aspects
The single dose toxicity and the repeated dose toxicity studies conducted on behalf of the applicant were GLP compliant. The GLP status of the studies reported from the published literature is unknown.

III.2 Pharmacology

III.2.1 Pharmacodynamics
No studies have been conducted. The process of coagulation involving the naturally occurring human proteins FVIII and VWF are well known.
III.2.2 Secondary pharmacodynamics
No studies.

III.2.3 Safety pharmacology
No studies.

III.2.4 Pharmacodynamic drug interactions
No studies.

III.2.5 Assessor’s comments
Optivate 100 IU/ml powder for solution for injection consists of naturally occurring human proteins. Their pharmacological actions are well known. Further studies are not required.

III.3 Pharmacokinetics
III.3.1 Pharmacokinetics - Optivate 100 IU/ml powder for solution for injection
No pharmacokinetics studies have been conducted with Optivate 100 IU/ml powder for solution for injection. The use of FVIII, a naturally occurring human protein in the blood, is not considered appropriate.

Information has been presented only on the excipients trehalose and polysorbate 20 and the potential trace contaminant, TnBP. The studies were conducted mainly in the rat, although the toxicological evaluation of the Optivate 100 IU/ml powder for solution for injection formulation itself was conducted in the mouse.

III.3.2 Pharmacokinetics - trehalose
In humans, trehalose is rapidly hydrolysed by the enzyme trehalase to its constituent glucose molecules, which can then be readily metabolised and excreted. Any trehalose not broken down is excreted directly into the urine.

In animals, there is varying degrees of trehalose breakdown, resulting in varying accounts of hydrolysis to glucose or direct excretion into urine. The rat has a poor metabolism of trehalose, with up to 87% recovered in the urine.

III.3.3 Pharmacokinetics - polysorbate 20 (polyoxyethylene (20) sorbitan monolaurate)
Polysorbate 20 is hydrolysed by blood lipases allowing the majority of the split moieties to be released in expired CO₂. Studies that were conducted in 1966/67 used ¹⁴C-labelled poloxymethylene or lauryl moieties administered orally or i.v. to the rat. The ¹⁴C-lauryl moiety appeared to be metabolised in a similar manner following either route of administration: the fatty ester bond was hydrolysed and the fatty acid metabolised. The ¹⁴C-poloxymethylene moiety was not metabolised since no radioactivity was recovered as ¹⁴C-CO₂; most appeared in the urine, but some was present in the faeces indicating biliary excretion.

III.3.4 Pharmacokinetics - TnBP
After intraperitoneal or oral administration of ¹⁴C-labelled TnBP, TnBP was extensively metabolised, mainly into dibutyl phosphate and monobutyl phosphate. Very little unmetabolised TnBP was found in the urine, the main excretory route.
III.3.5 Pharmacokinetic drug interactions
No studies.

III.3.6 Assessor’s comments
Optivate 100 IU/ml powder for solution for injection contains naturally occurring human plasma proteins, which are anticipated to behave in the same manner as naturally circulating proteins.

The pharmacokinetics of the excipients and potential trace contaminant have been evaluated through a review of the published literature.

III.4 Toxicology

Optivate 100 IU/ml powder for solution for injection contains naturally occurring human proteins formulated with some chemicals common in pharmaceuticals. It also contains two components, namely trehalose (a disaccharide of glucose) and the surfactant polysorbate 20. In addition TnBP may be present as a trace contaminant.

The toxicology programme was limited by the nature of the product itself with the limitation of immunogenic reaction to human protein in animals. Also since Optivate 100 IU/ml powder for solution for injection comprises a natural human protein for replacement therapy, the relevance of studies in normal (FVIII) replete animals is questionable. An excess of FVIII may be thrombogenic. The use of an animal model deficient in FVIII would not be appropriate since the effects of human FVIII would be lost due to immunogenicity.

Toxicity studies have been limited to one single-dose and one repeated-dose study in the mouse. For these studies Optivate 100 IU/ml powder for solution for injection was manufactured to a specific formulation to create two batches (8V359–single dose study and 8V373–repeated dose study) which had increased levels of the excipients trehalose and polysorbate 20. In addition, published data from toxicity studies carried out on the two excipients and TnBP have been reviewed.

III.4.1 Single dose toxicity

Single dose toxicity—Optivate 100 IU/ml powder for solution for injection
In this study, groups of 6 male and 6 female mice were administered a single intravenous (bolus) dose of the formulation at a dose of 5 mL/kg (which is 10x the dose volume required for a 50 IU/kg dose in humans) following which the animals were observed for 14 days.

The table below summarises the concentration of each constituent present in a standard batch of Optivate 100 IU/ml powder for solution for injection compared with that evaluated in this study.

<table>
<thead>
<tr>
<th>Table 1. Comparison of patient and toxicity study doses by component</th>
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<tbody>
<tr>
<td>Constituent</td>
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<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Optivate 50 IU/kg (0.5 ml/kg) patient dose</td>
</tr>
</tbody>
</table>

20
The table below summarises the concentration of each constituent present in a standard batch of Optivate 100 IU/ml powder for solution for injection compared with that evaluated in this study.

**Table 2. Comparison of patient and toxicity study doses by component**

<table>
<thead>
<tr>
<th>Constituent</th>
<th>Constituent concentration</th>
<th>Animal dose (5 ml/kg)</th>
<th>Animal dose compared with standard clinical dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor VIII</td>
<td>100 IU/ml</td>
<td>50 IU</td>
<td>X2</td>
</tr>
<tr>
<td>Protein</td>
<td>2.0 mg/ml</td>
<td>1.0 mg</td>
<td>X2</td>
</tr>
<tr>
<td>Trehalose (dihydrate)</td>
<td>30 mg/ml</td>
<td>15 mg</td>
<td>X20</td>
</tr>
<tr>
<td>Polysorbate 20</td>
<td>2 mg/ml</td>
<td>1 mg</td>
<td>X20</td>
</tr>
<tr>
<td>Sodium Chloride</td>
<td>300 mM</td>
<td>150 μmol</td>
<td>X6</td>
</tr>
<tr>
<td>Calcium Chloride</td>
<td>15 mM</td>
<td>7.5 μmol</td>
<td>X10</td>
</tr>
<tr>
<td>Citrate (trisodium)</td>
<td>10 mM</td>
<td>5 μmol</td>
<td>X10</td>
</tr>
</tbody>
</table>
### Conc. Amount/ kg Conc. Amount/kg

<table>
<thead>
<tr>
<th>Dose</th>
<th>2.5 mg/kg</th>
<th>1.0 mg/kg</th>
<th>2.5 ml/kg</th>
<th>1.0 ml/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor VIII</td>
<td>100 IU/ml</td>
<td>50 IU</td>
<td>20 IU/ml</td>
<td>50 IU</td>
</tr>
<tr>
<td>Protein</td>
<td>2.0 mg/ml</td>
<td>1.0 mg</td>
<td>0.4 mg/ml</td>
<td>1.0 mg</td>
</tr>
<tr>
<td>Trehalose (dihydrate)</td>
<td>30 mg/ml</td>
<td>15 mg</td>
<td>60 mg/ml</td>
<td>150 mg</td>
</tr>
<tr>
<td>Polysorbate 20</td>
<td>2 mg/ml</td>
<td>1 mg</td>
<td>4 mg/ml</td>
<td>10 mg</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>300 mM</td>
<td>150 μmol</td>
<td>190 μmol</td>
<td>475 μmol</td>
</tr>
<tr>
<td>Calcium chloride</td>
<td>15 mM</td>
<td>7.5 μmol</td>
<td>15 mM</td>
<td>37.5 μmol</td>
</tr>
<tr>
<td>Citrate (trisodium)</td>
<td>10 mM</td>
<td>5 μmol</td>
<td>10 mM</td>
<td>25 μmol</td>
</tr>
</tbody>
</table>

NB. TnBP concentration was not deliberately elevated. Standard specification is <1.7 mg/L, equivalent to <0.017 μg/IU FVIII

The only treatment related findings of toxicological significance were microscopic evidence of a slight local adverse reaction in the tissues adjacent to the tail vein (both dosage levels) and a low incidence of post-dosing overt signs of toxicity which consisted of piloerection, shivering and partially closed eyes generally from one to four hours post-dose. All other changes (prominent germinal centres in the spleen; tail lesions) were considered to be related to systemic exposure to a foreign protein or repeated venipuncture.

**Repeated dose toxicity – polysorbate 20**

WHO estimate than an acceptable daily intake (ADI) of polysorbate in humans is 25 mg/kg. A patient treated prophylactically with Optivate 100 IU/ml powder for solution for injection would receive approximately 0.5 mg/kg three times weekly. This is 50 times less than the ADI.

**Repeated dose toxicity – TnBP**

A review of literature apparently did not reveal any toxicological data following i.v. administration. A patient treated prophylactically with Optivate 100 IU/ml powder for solution for injection would receive not more than 0.0001 mg/kg three times a week. This is ≥800,000 times lower than the lowest dose with toxic effect in the literature, although it should be highlighted that the reported studies relate to oral or dermal route of administration.

**III.4.3 Genotoxicity**

**Genotoxicity – Optivate 100 IU/ml powder for solution for injection**

There have been no studies performed with Optivate 100 IU/ml powder for solution for injection.
**Genotoxicity – polysorbate 20**
Polysorbate 20 has been tested for genotoxicity in an Ames test, in a Bacillus subtilis rec-assay and in a cytogenetic test using hamster lung fibroblasts (Yam et al., 1984). It has also been tested in vivo in the micronucleus test (Jenssen and Ramel, 1980). There was no genotoxic activity in any test.

**Genotoxicity – TnBP**
In vitro studies have been conducted with TnBP. In bacterial systems TnBP was not mutagenic and it was not clastogenic in CHO cells.

**III.4.4 Carcinogenicity**

**Carcinogenicity – Optivate 100 IU/ml powder for solution for injection**
There have been no studies conducted with Optivate 100 IU/ml powder for solution for injection.

**Carcinogenicity – polysorbate 20**
A literature review by the expert panel of cosmetic, toiletry and fragrance association concluded that polysorbate 20 is not a carcinogen. This review included studies in the mouse, rat and hamster. Of all the studies reviewed, in one mouse study of 52 weeks duration, only a single benign dermal tumour occurred with an individual treated daily with dermal application of polysorbate 20, an effect not seen in any other animals in the study or other studies.

**Carcinogenicity – TnBP**
In an oral-dose rat carcinogenicity study, TnBP was not carcinogenic.

**III.4.5 Reproductive and development toxicity**

**Reproductive and developmental toxicity – Optivate 100 IU/ml powder for solution for injection**
There have been no studies conducted with Optivate 100 IU/ml powder for solution for injection. It is also not known whether Optivate 100 IU/ml powder for solution for injection can cause fetal harm when administered to pregnant women or can affect reproductive capacity. The SmPC (section 4.6) states that FVIII should be used during pregnancy and lactation only if clearly indicated.

**Reproductive and developmental toxicity – polysorbate 20**
No studies assessing the effect of polysorbate 20 on fertility and early embryonic development or pre and post-natal development have been reported.

A review of studies in rodents revealed that developmental toxicity in the rat occurred at >5000 mg/kg/day. This is approximately 10,000 times higher than the likely clinical daily dose.

**Reproductive and developmental toxicity – TnBP**
Studies assessing fertility and general reproductive performance and embryotoxicity have been reported. A review of studies revealed fetal toxicity in the rabbit at 400 mg/kg. The
maximal TnBP dose that could be administered to humans is <0.0000125 mg three times per week.

III.4.6 Local tolerance

Local tolerance – Optivate 100 IU/ml powder for solution for injection
No studies have been performed with Optivate 100 IU/ml powder for solution for injection. However in the 2 weeks repeated dose toxicity study, there was no evidence of adverse local reactions.

Local tolerance – polysorbate 20
In a review by the expert panel of cosmetic, toiletry and fragrance association, polysorbate 20 was well tolerated in guinea pigs (up to 3 g/kg percutaneously), rabbits (0.5 ml for 24 hours dermally) and humans (dermal occlusive patch for 72 hours).

III.4.7 Ecotoxicity/environmental risk assessment
A conventional ERA has not been submitted. The applicant argues that none of the chemicals used in the manufacture of Optivate 100 IU/ml powder for solution for injection are hazardous. The metabolites of Optivate 100 IU/ml powder for solution for injection are not considered to pose an environmental hazard. Also the estimated world-wide use of Optivate 100 IU/ml powder for solution for injection is likely to be a maximum of 900 L/yr.

III.4.8 SmPC
The SmPC is satisfactory.

III.4.9 Non-clinical expert
The non-clinical expert is a medical practitioner with experience in academic toxicology. this is satisfactory

III.5 Assessor’s overall conclusion
Optivate 100 IU/ml powder for solution for injection is prepared from human proteins and is produced by a similar process as the marketed product from the same company. Optivate 100 IU/ml powder for solution for injection is for replacement therapy. Therefore animal studies would not be useful in the assessment of safety. There is also the limitation of immunogenic reaction in animals.

In order to assess any potential direct or indirect toxic effects of the excipients polysorbate and trehalose the applicant conducted one single-dose and one repeated-dose toxicity studies of specially manufactured batches incorporating increased levels of these excipients. These studies confirmed their safety in use in this formulation.

In conclusion, the non-clinical data and information appear adequate for the type of product.
IV Clinical aspects
IV.1 Introduction
This is an MAA for the new medicinal product Optivate 100 IU/ml powder for solution for injection, which is a human plasma derived blood coagulation factor VIII (FVIII) product. In addition to FVIII the product also contains von Willebrand’s Factor (VWF). The applicants are the non-profit making blood fractionators BPL.

Optivate 100 IU/ml powder for solution for injection has been developed from a BPL product called 8Y (PL 08801/0021). This concentrate was also a complex of FVIII with its natural carrier protein, VWF. This product had been available since 1985. However, it was an intermediate purity FVIII product and had only one specific antiviral step in its manufacture. This step is the terminal dry heat at 80°C for 72 hours, which is known to be able to provide broad antiviral activity. The rationale for the development of Optivate 100 IU/ml powder for solution for injection was two-fold: (a) to produce a high purity FVIII and VWF complex and (b) to add an extra specific antiviral step to the manufacturing process.

Optivate 100 IU/ml powder for solution for injection is presented as a lyophilised product for reconstitution with sterilised water for injections which is supplied with the product. There are three presentations: a vial containing a nominal 250 IU of FVIII, one containing a nominal 500 IU of FVIII and one containing a nominal 1,000 IU of FVIII. To reconstitute the lyophilised powder for infusion 2.5 ml, 5 ml or 10 ml, respectively, of the sterilised water for injections Ph.Eur. is added. Thus the resulting solutions have identical concentrations of constituents.

The applicants are seeking an indication in this application for the treatment of patients with haemophilia A. They state that they intend to seek an indication for management of von Willebrand factor deficiency at a future date. However the presence of VWF in the product is of utility according to the applicants, since FVIII is a relatively unstable protein and, in a concentrate, requires stabilisation, usually with another protein excipient. The applicants argue that the protein VWF, acts as an endogenous stabiliser in vitro.

The new anti-viral step is a solvent/detergent process, utilising TnBP combined with polysorbate 20. The applicants state that this non-ionic surfactant was preferred to polysorbate 80 since it has a more rapid virucidal action, which they state is also directed against some non-lipid-enveloped viruses in addition to the lipid enveloped viruses for which S/D processes are normally aimed, and, in addition, it is stated to improve the solubility of the FVIII during the freeze-drying and the terminal dry heat processes. These measures are considered effective for enveloped viruses such as HIV, HBV and HCV, and for non-enveloped viruses HAV and parvovirus B19.

Optivate 100 IU/ml powder for solution for injection also contains the sugar trehalose as an excipient stabiliser.

Optivate 100 IU/ml powder for solution for injection has a high specific activity of FVIII, i.e. 800 IU/mg protein.
Type of application and regulatory background
This marketing authorisation was submitted as a standard abridged national application.

Clinical background
The clinical development of a plasma-derived FVIII for the European Community is guided by the CPMP Note for Guidance on Human Plasma Derived factor VIII and IX Products [2000], which became operational in April 2001. BPL have based their clinical development plan, for the use of Optivate 100 IU/ml powder for solution for injection in patients with haemophilia A, on this guideline. Several clinical studies for a new product are recommended:

a. a pharmacokinetic study in at least 12 patients, each over 12 years of age, with severe haemophilia A but without evidence of inhibitors, having had at least 20 exposures to a FVIII and who are not actively bleeding and have not received infusion of a concentrate for at least 3 days and preferably for 7 days;
b. a safety study in at least 50 previously treated patients (PTPs) with severe haemophilia A, over the age of 12 years, immunocompetent as indicated by a normal CD4 count (>400/μL) and who have had at least 150 exposures to a FVIII;
c. a study in at least 5 patients with haemophilia A undergoing at least 10 surgical procedures;
d. a study in 20 children under the age of 6 years to be started after the results of 20 adult PTPs are available;
e. documentation of any previously untreated patients (PUPs) who may receive treatment with the product.

Indications
Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).

Dose and dose regimen
The dose regimen and posology proposed in claimed indications are in line with the Core SPC guidance.

GCP aspects
BPL has stated that all clinical trials were conducted in accordance with Good Clinical Practice (GCP).

Orphan medicinal products
N/A

Paediatric development programme
According to Article 7 Paediatric Regulation EC 1901/2006 a PIP is not needed for Medicinal Products which have been developed and authorised before the paediatric regulation came into effect. However, paediatric data have been submitted in line with CPMP guidance described in section 1.2).

Scientific advice
The company has met MHRA and PEI for pre-submission advice in 2009.
Optivate 100 IU/mL powder for solution for injection

UK/H/4591/01/E01

Legal status
POM.

IV.2 Clinical trials
The clinical dossier comprises essentially the following four clinical trials:

- 8vWF PK: Pharmacokinetic study
- 8vWF SE: Safety and efficacy study
- 8vWF02: Surgery study
- 8vWF05: Study in children
- OSE: Study in other surgical procedures

Studies 8vWF PK and 8vWF SE were long term studies and studies 8vWF02 and 8vWF05 were surgical studies.

IV.2.1 Study 8vWF PK
This was a multicentre, international trial conducted to compare the pharmacokinetics and safety of Optivate 100 IU/ml powder for solution for injection with the patients’ current Factor VIII product. Trial centres were in the UK and Poland. The “comparator” comprised 6 different products (including a total of 9 different batches). Ten different batches of Optivate 100 IU/ml powder for solution for injection were employed as the test medication.

### Table 1: Outline of study 8vWF PK

|---------|------------|-----------------|-------|--------------|-----------|-----------|-------------------------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|

The trial employed an open design. Fifteen male Caucasian patients were recruited. Initially, a PK assessment was undertaken while the patients were administered their existing FVIII product using an intravenous (i.v.) bolus of 50 IU/kg infused at a rate of 10 ml per minute. This was followed by a similar assessment after the first administration of Optivate 100 IU/ml powder for solution for injection using the same dose. Patients were then treated with Optivate 100 IU/ml powder for solution for injection as their factor VIII product and the PK assessment was repeated after 3 months and after 6 months.

During the treatment phase, doses calculated to alleviate a bleed were in accordance with the guidelines given below.
Table 2: Guidelines for doses of factor VIII

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Plasma Concentration of Factor VIII desired in the subject’s blood immediately after infusion (IU per 100 ml)</th>
<th>Initial dose of Factor VIII (IU per kg bodyweight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor spontaneous haemorrhages, and muscle haematoma</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>Severe haemorrhage and muscle haematoma; haematuria. Minor surgery e.g. dental extractions, arthroscopy</td>
<td>40 to 50</td>
<td>20 to 25</td>
</tr>
</tbody>
</table>

**Inclusion criteria**

The following subjects were eligible for inclusion in the study:

- Subjects who had given written informed consent
- Subjects who were at least 12 years of age
- Previously treated patients (PTPs) with severe haemophilia A (<2% basal FVIII activity) without inhibitor to FVIII (<0.5 BU)
- Subjects who had had at least 3 days (if possible 7 days) since their last FVIII infusion
- Subjects who were currently receiving FVIII concentrate
- Subjects who required elective surgery within 6 months of starting Optivate 100 IU/ml powder for solution for injection treatment were eligible to be included in the study, providing that their surgery had been undertaken as part of the Optivate surgery study (trial code: 8vWF02).

**Exclusion criteria**

The following subjects were excluded from the study:

- Subjects who had had less than 20 exposures to FVIII concentrates
- Subjects who had a history of inhibitors to FVIII
- Subjects who were actively bleeding (such subjects were to be treated, as appropriate, and then asked to return after at least 3 days)
- Subjects who had an INR >1.5
- Subjects who had thrombocytopenia (platelets <50 x 10^9/L)
- Subjects who had clinically significant renal disease (serum creatinine >200 μmol/L)
- Subjects who had clinically significant liver disease (ALT levels greater than three times the upper normal limit)
- Subjects who were currently participating or had participated in another clinical trial within 30 days immediately prior to the study (with the exception of subjects that had participated in the Optivate surgery study (trial code: 8vWF02))
- Subjects who, in the opinion of the investigator, were unlikely to comply with the study protocol (e.g. drug/alcohol abuse)

**Primary endpoints**

The primary measure of comparable efficacy was the half-life calculated after visual inspection of the data for each subject to identify the terminal elimination phase (non-compartmental analysis). Results were tested for the normality of distribution using the Shapiro-Wilk test and if normality was confirmed, an analysis of variance was used to perform the comparison. Centre, subject within centre, and assessment (current FVIII, first Optivate assessment or second Optivate assessment) were included as explanatory variables in the statistical model.
Secondary endpoints
Secondary measures of efficacy were:
- Area under the concentration/time curve over 0 to 48 hours (AUC<sub>0-48</sub>)
- Incremental recovery at each pharmacokinetic cycle and at every batch change
- Clearance
- Mean residence time
- Alpha and beta half-life (estimates of half-life were derived from a two-compartment model fitted using WinNonLin Professional, Version 1.5. Scientific Consulting Inc, North Carolina, USA)

Safety was assessed by reported adverse events (AEs), by screening for viral markers and by the usual haematological and biochemical laboratory assessments.

Pharmacokinetic results
Thirteen patients had a complete data set for the three assessments. One patient had no data following the first bolus of Optivate 100 IU/ml powder for solution for injection and one had insufficient data for the comparator infusion. A further patient’s data for the comparator regimen were potentially considered unreliable as the samples could have been thawed prior to analysis. As the data appeared consistent across this patient, data from this individual were however included in the analysis.

All patients were male Caucasians; the mean age was 31 years (range 20–48). Mean duration of FVIII use was 10 years (range 20–48). FVIII products used in the last 12 months are summarised below. The most frequently used products were FVIII by Baxter, and Koate, each of which had been used by eight subjects.

Table 3: FVIII products used in previous 12 months

<table>
<thead>
<tr>
<th>Product</th>
<th>Prophylactic use</th>
<th>Spontaneous use</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CZYMNIK VIII</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>FACTOR VIII (BPL)</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Factor VIII (Baxter)</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Fandri</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Koate</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Replente</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total use of products</td>
<td>10</td>
<td>13</td>
<td>23</td>
</tr>
</tbody>
</table>

The results are summarised in table 4. As there was no statistical difference between the results of the two PK profiles for Optivate 100 IU/ml powder for solution for injection, the data have been combined (table 5).

Table 4: Comparison of all patient PK data (N=14 or 15) with data from the same cohort of patients (N=13) and between different products and PK assessments
Table 5: Consolidated data summary for Optivate (PK1 and PK2)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>n</th>
<th>Mean</th>
<th>Median</th>
<th>SEM</th>
<th>Min</th>
<th>Max</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-compartmental half-life (h)</td>
<td>15</td>
<td>12.38</td>
<td>12.26</td>
<td>0.67</td>
<td>7.51</td>
<td>17.59</td>
<td>10.94</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>13.83</td>
</tr>
<tr>
<td>AUC 0→inf (h.IU/mL)</td>
<td>15</td>
<td>16.13</td>
<td>14.33</td>
<td>1.01</td>
<td>11.37</td>
<td>22.53</td>
<td>13.97</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18.28</td>
</tr>
<tr>
<td>AUC 0→α (h.IU/mL)</td>
<td>15</td>
<td>17.31</td>
<td>15.23</td>
<td>1.09</td>
<td>11.77</td>
<td>25.68</td>
<td>14.98</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>19.65</td>
</tr>
<tr>
<td>Clearance (mL/kg/h)</td>
<td>15</td>
<td>3.11</td>
<td>3.26</td>
<td>0.19</td>
<td>1.96</td>
<td>4.39</td>
<td>2.71</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.51</td>
</tr>
<tr>
<td>Mean Residence Time (h)</td>
<td>15</td>
<td>17.45</td>
<td>17.23</td>
<td>0.68</td>
<td>12.40</td>
<td>23.39</td>
<td>15.59</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18.92</td>
</tr>
<tr>
<td>Volume of distribution (mL per kg)</td>
<td>15</td>
<td>53.36</td>
<td>55.26</td>
<td>3.34</td>
<td>34.50</td>
<td>75.59</td>
<td>46.20</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60.52</td>
</tr>
<tr>
<td>Alpha half life (h)</td>
<td>11</td>
<td>2.18</td>
<td>2.17</td>
<td>0.32</td>
<td>0.55</td>
<td>3.50</td>
<td>1.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.88</td>
</tr>
<tr>
<td>Beta half life (h)</td>
<td>15</td>
<td>12.63</td>
<td>12.47</td>
<td>0.61</td>
<td>7.35</td>
<td>17.08</td>
<td>11.33</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>13.92</td>
</tr>
<tr>
<td>Recovery (IU/mL per IU/kg)</td>
<td>15</td>
<td>0.0248</td>
<td>0.0247</td>
<td>0.0012</td>
<td>0.0196</td>
<td>0.0342</td>
<td>0.0222</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0274</td>
</tr>
</tbody>
</table>

Treatment of spontaneous bleeds

In the long-term study, patients were managed either with prophylaxis or with on demand treatment. They were followed-up for a median of 98 weeks. The summary of the statistics on the treatment of bleeds is presented in table 6.

The doses used per bleed in the prophylactic modality of treatment were higher than with on demand use but with an overall reduction of the incidence of bleeding episodes, and in the
majority of the cases, the clinical response was assessed by the physician and the patient as “excellent-good” or “very helpful-helpful”, respectively.

Table 6: Treatment of bleeds (new and ongoing) in the prophylactic use group in 8vWF PK (n=6)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of bleeds per subject</td>
<td>20.67</td>
<td>22.00</td>
<td>ND</td>
<td>3.00</td>
<td>38.00</td>
<td>5.54</td>
<td>35.80</td>
</tr>
<tr>
<td>No. of infusions per week per subject</td>
<td>0.31</td>
<td>0.30</td>
<td>0.27</td>
<td>0.03</td>
<td>0.76</td>
<td>0.03</td>
<td>0.59</td>
</tr>
<tr>
<td>No. of infusions per month per subject</td>
<td>1.23</td>
<td>1.20</td>
<td>1.08</td>
<td>0.12</td>
<td>3.06</td>
<td>0.10</td>
<td>2.37</td>
</tr>
<tr>
<td>Total dose per bleed per subject (IU/kg)</td>
<td>25.90</td>
<td>25.56</td>
<td>ND</td>
<td>15.20</td>
<td>35.61</td>
<td>17.35</td>
<td>34.44</td>
</tr>
<tr>
<td>Total dose per month per subject (IU/kg)</td>
<td>22.64</td>
<td>24.93</td>
<td>16.73</td>
<td>1.88</td>
<td>42.73</td>
<td>5.08</td>
<td>40.19</td>
</tr>
<tr>
<td>Dose per year per subject (IU/kg)</td>
<td>295.12</td>
<td>324.96</td>
<td>218.02</td>
<td>24.52</td>
<td>556.50</td>
<td>66.32</td>
<td>523.91</td>
</tr>
<tr>
<td>Total dose per subject (IU/kg)</td>
<td>566.19</td>
<td>595.69</td>
<td>431.35</td>
<td>45.60</td>
<td>1118.57</td>
<td>131.52</td>
<td>1018.86</td>
</tr>
</tbody>
</table>

Table 7: Treatment of bleeds (new and ongoing) in the on-demand use group in 8vWF PK (n=9)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of bleeds per subject</td>
<td>99.56</td>
<td>106.00</td>
<td>34.08</td>
<td>51.00</td>
<td>150.00</td>
<td>73.36</td>
<td>125.75</td>
</tr>
<tr>
<td>No. of infusions per week per subject</td>
<td>1.37</td>
<td>1.67</td>
<td>0.53</td>
<td>0.59</td>
<td>1.90</td>
<td>0.97</td>
<td>1.78</td>
</tr>
<tr>
<td>No. of infusions per month per subject</td>
<td>5.49</td>
<td>6.69</td>
<td>2.11</td>
<td>2.37</td>
<td>7.62</td>
<td>3.87</td>
<td>7.11</td>
</tr>
<tr>
<td>Total dose per bleed per subject (IU/kg)</td>
<td>20.57</td>
<td>18.54</td>
<td>3.87</td>
<td>15.37</td>
<td>25.42</td>
<td>17.58</td>
<td>23.55</td>
</tr>
<tr>
<td>Total dose per month per subject (IU/kg)</td>
<td>83.44</td>
<td>82.98</td>
<td>31.97</td>
<td>43.68</td>
<td>146.50</td>
<td>58.86</td>
<td>108.01</td>
</tr>
<tr>
<td>Dose per year per subject (IU/kg)</td>
<td>1088.28</td>
<td>1081.68</td>
<td>417.32</td>
<td>569.55</td>
<td>1913.16</td>
<td>767.49</td>
<td>1409.06</td>
</tr>
<tr>
<td>Total dose per subject (IU/kg)</td>
<td>2020.67</td>
<td>1920.19</td>
<td>768.80</td>
<td>1059.36</td>
<td>3558.48</td>
<td>1429.72</td>
<td>2611.62</td>
</tr>
</tbody>
</table>

**Safety**

A total of 129 AEs were reported by 13 of the 15 patients (87%). A summary of AEs is presented in table 8. One subject reported one AE while receiving previous FVIII treatment, and 13 subjects reported a total of 129 AEs while receiving Optivate 100 IU/ml powder for solution for injection in this long-term study.

There were no deaths.

Two AEs were categorised as serious; both were hospitalisations for a surgical procedure to the knee (subjects 112 and 111). The events were considered by the clinicians to be unrelated to Optivate 100 IU/ml powder for solution for injection.
Eight AEs were rated as severe, all reported during Optivate 100 IU/ml powder for solution for injection treatment. None were considered to be related to the study drug. These were: an ear infection in subject 109, knee pain, migraine, pain in lower sternum and ribs, pain in right ankle, pain due to bleed in right ankle, and headache, all reported for subject 110, and a left knee operation in subject 111. In each case the subject recovered with no residual effects.

Adverse events recorded as possibly or probably related to Optivate 100 IU/ml powder for solution for injection were regarded as study drug-related adverse drug reactions. Three such AEs were recorded. The three study drug-related adverse reactions were reported by subject 104. The first event, itching, was reported two weeks after starting Optivate 100 IU/ml powder for solution for injection therapy. During stage 2 of the study, subject 104 reported slight contusion of the left thigh (second event). The following day the subject reported the third AE, slight oedema of the left thigh. All 3 events were rated mild in severity, occurred after infusion of Optivate 100 IU/ml powder for solution for injection and cleared up within 24 hours. The subject recovered with no residual effects and with no treatment being given in all cases.

Table 8: Adverse events reported with Optivate use by two or more subjects

<table>
<thead>
<tr>
<th>ADVERSE EVENTS (MedDRA preferred term)</th>
<th>Prophylactic use</th>
<th>Spontaneous use</th>
<th>Total use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of weeks treatment per subject</td>
<td>98.6</td>
<td>97.3</td>
<td>97.8</td>
</tr>
<tr>
<td>Toothache</td>
<td>0</td>
<td>2 (22%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Abdominal pain NOS</td>
<td>2 (33%)</td>
<td>0</td>
<td>2 (15%)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>1 (17%)</td>
<td>1 (11%)</td>
<td>2 (15%)</td>
</tr>
<tr>
<td>Influenza like illness</td>
<td>2 (33%)</td>
<td>0</td>
<td>2 (15%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>2 (33%)</td>
<td>0</td>
<td>2 (15%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>3 (50%)</td>
<td>1 (11%)</td>
<td>4 (27%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection NOS</td>
<td>0</td>
<td>2 (22%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Limb injury NOS</td>
<td>1 (17%)</td>
<td>1 (11%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3 (50%)</td>
<td>0</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>2 (33%)</td>
<td>0</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Headache NOS</td>
<td>3 (50%)</td>
<td>3 (33%)</td>
<td>6 (40%)</td>
</tr>
</tbody>
</table>

The most frequently reported AEs in the Optivate period were headache (44 reports made by 6 subjects), arthralgia (13 reports made by 3 subjects), and nasopharyngitis (9 reports made by 4 subjects). No other events were reported by more than two subjects. None of the above AEs were reported to be related to the study medication.

No seroconversions were recorded for the usual blood borne viruses or surrogate markers. No significant haematological or biochemical changes were observed.

Assessor’s comments and conclusion

The applicants have complied with the relevant CPMP guideline, which requires repeated PK data in at least 12 patients using at least 3 different batches.

However, the recovery was measured on samples up to 90 mins after injection rather than the 3 hours recommended in the guideline. This difference in the trial design compared to the
guide a consequence of a general change in practice and is not likely to impact adversely on the results achieved and on the conclusions of the trial.

Optivate 100 IU/ml powder for solution for injection appears to have the PK characteristics of a plasma-derived FVIII. There is no identified safety concern. The PK parameters are similar after 6 months of use, suggesting that inhibitors were not produced in the patients studied during this time.

IV.2.2 Study 8vWFSE

This trial was an open label multicentre international trial conducted in centres in the UK and Poland. The report presented comprises the first phase of the study where Optivate 100 IU/ml powder for solution for injection was received for 6 months.

Table 9: Outline of study

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Number of Study Centres</th>
<th>Study Centres</th>
<th>Sample size</th>
<th>Design</th>
<th>Study Purpose</th>
<th>Study Objectives</th>
<th>PK parameters</th>
<th>Duration</th>
<th>Number of patients</th>
<th>Diagnosis</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>8vWFSE</td>
<td>11 centres</td>
<td>13/19/5/51</td>
<td>Multiple</td>
<td>open, non-randomised, non-comparative, prospective study</td>
<td>Study the recovery, safety and efficacy of OPTIVATE® in long-term use, either prophylactically or on demand</td>
<td>55 patients treated with OPTIVATE® 2 years dosed as per previous Factor VIII therapy</td>
<td>Number of patients treated with OPTIVATE® 2 years aged as per previous Factor VIII therapy</td>
<td>Median age</td>
<td>Severe Haemophilia A (&lt;2% basal FVIII activity)</td>
<td>Numbers, type and severity of bleed and achievement of haemostasis</td>
<td>Assessments of treatment for patients treated prophylactically and on demand therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>UK Centres</td>
<td>Manchaster</td>
<td>London</td>
<td>Study Centres</td>
<td>Study the recovery, safety and efficacy of OPTIVATE® in long-term use, either prophylactically or on demand</td>
<td>Number of patients treated with OPTIVATE® 2 years aged as per previous Factor VIII therapy</td>
<td>Median age</td>
<td>Severe Haemophilia A (&lt;2% basal FVIII activity)</td>
<td>Numbers, type and severity of bleed and achievement of haemostasis</td>
<td>Assessments of treatment for patients treated prophylactically and on demand therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cambridge</td>
<td>Nottingham</td>
<td>Southampton</td>
<td>Study the recovery, safety and efficacy of OPTIVATE® in long-term use, either prophylactically or on demand</td>
<td>Number of patients treated with OPTIVATE® 2 years aged as per previous Factor VIII therapy</td>
<td>Number of patients treated with OPTIVATE® 2 years aged as per previous Factor VIII therapy</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Leeds</td>
<td>Sheffield</td>
<td>Oxford</td>
<td>Study the recovery, safety and efficacy of OPTIVATE® in long-term use, either prophylactically or on demand</td>
<td>Number of patients treated with OPTIVATE® 2 years aged as per previous Factor VIII therapy</td>
<td>Number of patients treated with OPTIVATE® 2 years aged as per previous Factor VIII therapy</td>
<td>Median age</td>
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<td>Numbers, type and severity of bleed and achievement of haemostasis</td>
<td>Assessments of treatment for patients treated prophylactically and on demand therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Liverpool</td>
<td>London</td>
<td>Birmingham</td>
<td>Study the recovery, safety and efficacy of OPTIVATE® in long-term use, either prophylactically or on demand</td>
<td>Number of patients treated with OPTIVATE® 2 years aged as per previous Factor VIII therapy</td>
<td>Number of patients treated with OPTIVATE® 2 years aged as per previous Factor VIII therapy</td>
<td>Median age</td>
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<tr>
<td></td>
<td></td>
<td>Manchester</td>
<td>London</td>
<td>Sheffield</td>
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<tr>
<td></td>
<td></td>
<td>Cambridge</td>
<td>London</td>
<td>Sheffield</td>
<td>Study the recovery, safety and efficacy of OPTIVATE® in long-term use, either prophylactically or on demand</td>
<td>Number of patients treated with OPTIVATE® 2 years aged as per previous Factor VIII therapy</td>
<td>Number of patients treated with OPTIVATE® 2 years aged as per previous Factor VIII therapy</td>
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<td></td>
<td></td>
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<td>Sheffield</td>
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<td></td>
<td></td>
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<td>London</td>
<td>Sheffield</td>
<td>Study the recovery, safety and efficacy of OPTIVATE® in long-term use, either prophylactically or on demand</td>
<td>Number of patients treated with OPTIVATE® 2 years aged as per previous Factor VIII therapy</td>
<td>Number of patients treated with OPTIVATE® 2 years aged as per previous Factor VIII therapy</td>
<td>Median age</td>
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<tr>
<td></td>
<td></td>
<td>Manchester</td>
<td>London</td>
<td>Sheffield</td>
<td>Study the recovery, safety and efficacy of OPTIVATE® in long-term use, either prophylactically or on demand</td>
<td>Number of patients treated with OPTIVATE® 2 years aged as per previous Factor VIII therapy</td>
<td>Number of patients treated with OPTIVATE® 2 years aged as per previous Factor VIII therapy</td>
<td>Median age</td>
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<tr>
<td></td>
<td></td>
<td>Manchester</td>
<td>London</td>
<td>Sheffield</td>
<td>Study the recovery, safety and efficacy of OPTIVATE® in long-term use, either prophylactically or on demand</td>
<td>Number of patients treated with OPTIVATE® 2 years aged as per previous Factor VIII therapy</td>
<td>Number of patients treated with OPTIVATE® 2 years aged as per previous Factor VIII therapy</td>
<td>Median age</td>
<td>Severe Haemophilia A (&lt;2% basal FVIII activity)</td>
<td>Numbers, type and severity of bleed and achievement of haemostasis</td>
<td>Assessments of treatment for patients treated prophylactically and on demand therapy</td>
</tr>
</tbody>
</table>

The objective of the study was to assess the safety and efficacy of Optivate 100 IU/ml powder for solution for injection in previously treated haemophiliacs (PTPs). Fifty-five patients with severe haemophilia were enrolled. All were at least 12 years of age and had received products other than Optivate 100 IU/ml powder for solution for injection at an exposure >150 treatment days in total. Patients were inhibitor-free (< 5BU).

**Inclusion criteria**

The following subjects were eligible for inclusion in the study:

- Subjects who had given written informed consent
- Subjects who were at least 12 years of age
- Previously treated patients (PTPs) with severe haemophilia A <2% basal FVIII activity) without inhibitor to FVIII <0.5 BU)
- Subjects who were immunocompetent (CD4 lymphocytes >0.4 x 10⁹ / 1)
- Subjects who required elective surgery in 6 months of starting on Optivate 100 IU/ml powder for solution for injection were eligible to be included in the study, providing that their surgery could be undertaken as part of the Optivate surgery study (trial code 8vWF02)
Exclusion criteria
The following subjects were excluded from the study:
- Subjects who had less than 150 treatment exposure days to FVIII concentrates
- Subjects who had a history of inhibitors to FVIII (>0.5 BU)
- Subjects who had an INR >1.5
- Subjects who had thrombocytopenia (platelets <50 x 10^9/L)
- Subjects who had clinically significant renal disease (creatinine >200 mol/L)
- Subjects who had clinically significant liver disease (ALT levels greater than three times the upper normal limit)
- Subjects who were currently participating or had participated in another clinical study within the last 30 days prior to study entry (with the exception of subjects who participated in the Optivate surgery study; trial code: 8vWF02)
- Subjects who, in the opinion of the investigator, were unlikely to comply with the study protocol (e.g. drug/alcohol abuse)

Endpoints
Following recruitment and screening, patients were commenced on Optivate 100 IU/ml powder for solution for injection at the same dose as their current FVIII product. Recovery was assessed. Further assessment of recovery was undertaken following 3 and 6 months of treatment and this comprised the primary outcome variable (recovery assessments were also undertaken at changes of product batch). Patients utilised the product in line with their usual practice i.e. either prophylactically or for the treatment of bleeding (“spontaneous use”).

The number and severity of bleeds was recorded, as was an assessment of the satisfactory nature or otherwise of haemostasis.

Safety was assessed by recording AEs. Laboratory safety included serology for blood borne viruses and routine biochemistry and haematology was also undertaken.

Efficacy results
Recovery
Mean recovery showed no decrease with treatment being 2.72 (95% CI 2.52, 2.92) IU/dL per IU/kg at week 0 and 2.60 (95% CI 2.38, 2.82) IU/dL per IU/kg at week 12.

Treatment of bleeds
The summary of the statistics on bleeds according to the type of use is presented in tables 10 and 11.
Table 10: Treatment of bleeds (new and ongoing) for subjects in the prophylactic use group in 8vWFSE (n=5)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of bleeds per subject</td>
<td>26.80</td>
<td>11.00</td>
<td>30.97</td>
<td>2.00</td>
<td>70.00</td>
<td>-11.67</td>
<td>65.27</td>
</tr>
<tr>
<td>Infusions per week per subject</td>
<td>0.47</td>
<td>0.16</td>
<td>0.57</td>
<td>0.02</td>
<td>1.33</td>
<td>-0.24</td>
<td>1.18</td>
</tr>
<tr>
<td>Infusions per month per subject</td>
<td>1.88</td>
<td>0.64</td>
<td>2.29</td>
<td>0.08</td>
<td>5.34</td>
<td>-0.96</td>
<td>4.73</td>
</tr>
<tr>
<td>Dose / bleed per subject (IU/kg)</td>
<td>60.12</td>
<td>42.61</td>
<td>56.21</td>
<td>19.14</td>
<td>156.90</td>
<td>-9.67</td>
<td>129.91</td>
</tr>
<tr>
<td>Dose / month per subject (IU/kg)</td>
<td>38.99</td>
<td>12.31</td>
<td>50.65</td>
<td>4.82</td>
<td>126.31</td>
<td>-23.89</td>
<td>101.88</td>
</tr>
<tr>
<td>Dose per year per subject (IU/kg)</td>
<td>508.39</td>
<td>160.93</td>
<td>660.64</td>
<td>62.95</td>
<td>1647.61</td>
<td>-311.90</td>
<td>1328.68</td>
</tr>
<tr>
<td>Total dose per subject (IU/kg)</td>
<td>923.30</td>
<td>313.82</td>
<td>1193.01</td>
<td>115.20</td>
<td>2982.17</td>
<td>-558.01</td>
<td>2404.62</td>
</tr>
</tbody>
</table>

Table 11: Treatment of bleeds (new and ongoing) for subjects in the spontaneous use group in 8vWFSE (n=50)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of bleeds per subject</td>
<td>65.10</td>
<td>64.00</td>
<td>43.27</td>
<td>2.00</td>
<td>184.00</td>
<td>52.81</td>
<td>77.39</td>
</tr>
<tr>
<td>Infusions per week per subject</td>
<td>0.95</td>
<td>0.93</td>
<td>0.55</td>
<td>0.07</td>
<td>2.25</td>
<td>0.79</td>
<td>1.11</td>
</tr>
<tr>
<td>Infusions per month per subject</td>
<td>3.80</td>
<td>3.72</td>
<td>2.20</td>
<td>0.30</td>
<td>8.98</td>
<td>3.17</td>
<td>4.42</td>
</tr>
<tr>
<td>Dose / bleed per subject (IU/kg)</td>
<td>27.01</td>
<td>21.87</td>
<td>15.91</td>
<td>7.95</td>
<td>82.51</td>
<td>22.49</td>
<td>31.52</td>
</tr>
<tr>
<td>Dose / month per subject (IU/kg)</td>
<td>71.03</td>
<td>61.44</td>
<td>50.03</td>
<td>6.11</td>
<td>189.51</td>
<td>56.81</td>
<td>85.25</td>
</tr>
<tr>
<td>Dose per year per subject (IU/kg)</td>
<td>925.72</td>
<td>801.26</td>
<td>651.33</td>
<td>79.58</td>
<td>2465.62</td>
<td>740.62</td>
<td>1110.83</td>
</tr>
<tr>
<td>Total dose per subject (IU/kg)</td>
<td>1658.58</td>
<td>1445.39</td>
<td>1280.80</td>
<td>106.00</td>
<td>4635.36</td>
<td>1294.58</td>
<td>2022.58</td>
</tr>
</tbody>
</table>

The mean number of bleeds was 26.80 for those using the product prophylactically and 65.10 for those using it for spontaneous use only. The median dose per bleed (new and ongoing) per subject was 60.12 and 27.01 IU/kg respectively. Bleed severity was rated as major in 42% of the episodes in patients using the product prophylactically and 40% of the episodes in the spontaneous users.

Patients rated response of the acceptability of haemostasis mirrored that undertaken by the investigators. For the patient assessment, the product was rated as very helpful in 58% and helpful in 41% of bleeds in the prophylactic group and in 34% and 57% respectively of the spontaneous users.

**Safety**

**Adverse events**

Forty-six patients reported a total of 355 AEs. The six most frequently reported AEs in the Optivate period were headache (67 reports made by 15 subjects), arthralgia (32 reports made by 10 subjects), toothache (14 reports made by 6 subjects), pyrexia (10 reports made by 7 subjects), nausea (10 reports in 4 subjects) and tooth extraction NOS (10 reported in 7 subjects).
Nineteen were assessed as drug related as follows: headache, vertigo, infusions site erythema, musculoskeletal stiffness, pyrexia, somnolence and rigors. The most frequently reported adverse drug reactions were headache (7 reports in 3 subjects) and vertigo (4 reports in 2 subjects). All except one resolved within one day.

There were 27 serious adverse events (SAEs) reported during the whole study, all were hospitalisations. Twenty of these SAEs were for surgical interventions: 8 were included in the formal surgical report; the others are detailed in a report titled ‘Other Surgical Experiences with Optivate 100 IU/ml powder for solution for injection. One SAE was reported between pre-study and week 0 (subject 314, hospitalisation for liver biopsy), and another was a fatal, CNS (Central Nervous System) bleed (see details below). All the SAEs were considered to be unrelated to Optivate 100 IU/ml powder for solution for injection and their narratives were provided.

Twenty-three AEs were rated as severe; all were reported during Optivate 100 IU/ml powder for solution for injection treatment. None were considered to be related to the study drug.

Deaths
Two months after completing Stage 1 of the study, patient 308 died due to a cerebral haemorrhage complicated by renal failure. This event was considered by the clinician to be unrelated to Optivate treatment.

Other serious adverse events (SAEs)
Sixteen subjects reported a total of 26 other SAEs; all were hospitalisations and considered to be unrelated to Optivate by the physician. One subject (306) reported eight SAEs. All narratives were provided in the CSR and indicated that most of SAEs included hospitalisations for surgery, bleeding episodes or injuries.

Subject 306, enrolled at the Manchester centre, reported eight SAEs all concerning orthopaedic interventions to the knee joint and related to his pre-existing medical condition. Four of the procedures were conducted under the surgery protocol (8vWF02). All the SAEs were considered to be unrelated to Optivate 100 IU/ml powder for solution for injection.

No seroconversion to blood borne viruses or significant laboratory abnormality was reported.

Assessor’s comments and conclusion
The assessment of 8vWFSE study indicates that overall efficacy and safety of Optivate 100 IU/ml powder for solution for injection has been shown. The mean doses of the agent used for both prophylactic and on-demand treatment is within the core SPC requirement for plasma-derived FVIII products. The safety profile has not shown new safety signals. None of the patient in this study has had a positive inhibitor test during the entire study period.

Intracranial bleeding is known as a rare SAE in patients with haemophilia and is included in the SmPC of other FVIII products. However there is a concern over the young age of the patient. The history of hypertension and long-standing haemophilia suggest that this patient had a high baseline risk of intracranial bleeding. The inhibitor screening was negative. This patient had been on on-demand treatment with Optivate 100 IU/ml powder for solution for injection. The intracranial bleeding episode is most likely attributed to hypertension.
The incidence of vertigo and headache even reported previously with the use of other coagulation factors appears to be very common. The applicant states that the number of these reports fall within the common range ($\geq 1/100$ to $<1/10$) of AE frequencies in regulatory guidelines. This is acceptable. The somnolence is an unusual symptom. The applicant states that in neither of the two subjects reporting lethargy was there any suggestion that hypersensitivity reactions had occurred in relation to these symptoms or with any other Optivate infusion.

Overall, the study satisfies the CPMP guideline in relation to PTPs. The product appears efficacious and safe in respect of inhibitor formation, viral safety and general safety.

**IV.2.3 Study 8vWF02**
This was a multicentre, international trial conducted in centres in the UK and Poland. The objective of the study was to ascertain the safety and efficacy of Optivate 100 IU/ml powder for solution for injection in patients undergoing surgery.

The study was open and non-comparative. Six patients were recruited who underwent 9 surgical procedures (one with 2 stages) which included orthopaedic operations such as total knee replacement, liver biopsy and dental surgery including extractions.

Following a pre-study screen, patients received Optivate 100 IU/ml powder for solution for injection calculated to raise FVIII level to 100%. FVIII levels were assayed up to 90 minutes after the dose and twice daily between days 2 and 10 until patient discharge. Optivate 100 IU/ml powder for solution for injection was administered after this initial bolus at the discretion of the investigators to keep FVIII levels $>50$.

Evaluation criteria comprised recovery after the bolus dose, and the efficacy of haemostasis. Safety data recorded included AEs, laboratory safety and serology to the usual blood borne viruses.

**Results**
Overall results are shown below.
The mean pre-operative bolus dose was 51.6 IU/kg (48.6–54.0). All but one patient received another bolus on the day of the operation (mean dose = 26.1 IU/kg). The dosage of Optivate 100 IU/ml powder for solution for injection on the day of operation ranged from 54 to 105 IU/kg; the mean was 76.3 IU/kg. In the following days the daily dose decreased from a mean of 51.9 on Day 2 to about 30 IU/kg on Day 6. Treatment duration at the hospital ranged from 3 to 10 days depending on the procedure. During this period, only 9 pre-bolus assays showed values less than the therapeutic target of 50% (or 50 IU/dL); they were all measured in the morning. The mean cumulative dose used was 260.4 IU/kg. The individual doses of Optivate 100 IU/ml powder for solution for injection are summarised in tables 13–15.

Mean incremental recovery was 2.90 IU/dL per IU/kg and ranged from 2.37 to 3.41 IU/dL per IU/kg. Low values of FVIII in the post operative phase were not associated with bleeding. No unusual blood loss was reported during the operation or in the post-operative period. No patient received tranexamic acid as stipulated in the protocol. Haemostasis was satisfactory in all procedures. One patient received transfusion, but this was necessitated by pre-operative anaemia caused by hiatus hernia, ulcerative colitis and haemorrhoids.

Table 13: Daily dosage of Optivate (IU) used in surgical procedures requiring ‘short term’ use (less than 5 days)

<table>
<thead>
<tr>
<th>Procedure no. and Statistics</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
<th>Day 8</th>
<th>Day 9</th>
<th>Day 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>202</td>
<td>6,380</td>
<td>4,400</td>
<td>2,200</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>203</td>
<td>5,500</td>
<td>4,400</td>
<td>2,200</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>206</td>
<td>4,500</td>
<td>5,000</td>
<td>5,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>207</td>
<td>5,000</td>
<td>3,500</td>
<td>4,500</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>208</td>
<td>4,320</td>
<td>2,160</td>
<td>2,160</td>
<td>2,700</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>5,140</td>
<td>3,892</td>
<td>3,212</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Median</td>
<td>5,000</td>
<td>4,400</td>
<td>2,200</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Minimum</td>
<td>4,320</td>
<td>2,160</td>
<td>2,160</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Maximum</td>
<td>6,380</td>
<td>5,000</td>
<td>5,000</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>
Table 14: Daily dosage of Optivate (IU) used in surgical procedures requiring ‘long term’ use (more than 5 days)

<table>
<thead>
<tr>
<th>Procedure no. and Statistics</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
<th>Day 8</th>
<th>Day 9</th>
<th>Day 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>201</td>
<td>10,000</td>
<td>5,000</td>
<td>4,000</td>
<td>4,000</td>
<td>4,000</td>
<td>4,000</td>
<td>3,000</td>
<td>3,000</td>
<td>3,000</td>
<td>3,000</td>
</tr>
<tr>
<td>204</td>
<td>6,110</td>
<td>3,570</td>
<td>3,060</td>
<td>3,060</td>
<td>3,060</td>
<td>2,550</td>
<td>1,020</td>
<td>3,000</td>
<td>3,000</td>
<td>3,000</td>
</tr>
<tr>
<td>209</td>
<td>6,480</td>
<td>3,780</td>
<td>3,240</td>
<td>3,240</td>
<td>3,240</td>
<td>3,240</td>
<td>1,620</td>
<td>3,000</td>
<td>3,000</td>
<td>3,000</td>
</tr>
<tr>
<td>210</td>
<td>6,480</td>
<td>4,320</td>
<td>4,320</td>
<td>4,320</td>
<td>4,320</td>
<td>3,780</td>
<td>3,240</td>
<td>3,240</td>
<td>3,240</td>
<td>3,240</td>
</tr>
<tr>
<td>211</td>
<td>6,300</td>
<td>4,200</td>
<td>4,200</td>
<td>4,200</td>
<td>4,200</td>
<td>3,150</td>
<td>3,150</td>
<td>3,150</td>
<td>3,150</td>
<td>3,150</td>
</tr>
<tr>
<td>Median</td>
<td>6,480</td>
<td>4,200</td>
<td>4,000</td>
<td>4,000</td>
<td>4,000</td>
<td>3,000</td>
<td>3,075</td>
<td>3,120</td>
<td>3,120</td>
<td>3,120</td>
</tr>
<tr>
<td>Minimum</td>
<td>6,110</td>
<td>3,570</td>
<td>3,060</td>
<td>3,060</td>
<td>3,060</td>
<td>1,620</td>
<td>1,020</td>
<td>3,000</td>
<td>3,000</td>
<td>3,000</td>
</tr>
<tr>
<td>Maximum</td>
<td>10,000</td>
<td>5,000</td>
<td>4,320</td>
<td>4,320</td>
<td>4,320</td>
<td>3,780</td>
<td>3,240</td>
<td>3,240</td>
<td>3,240</td>
<td>3,240</td>
</tr>
</tbody>
</table>

Table 15: Individual cumulative amounts of Optivate used per procedure

<table>
<thead>
<tr>
<th>Procedure no.</th>
<th>Patient weight (kg)</th>
<th>Procedure</th>
<th>Duration (days)</th>
<th>Total dose (IU)</th>
<th>Total dose (IU/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>202</td>
<td>83.0</td>
<td>Liver biopsy</td>
<td>3</td>
<td>12,980</td>
<td>156.4</td>
</tr>
<tr>
<td>203</td>
<td>73.0</td>
<td>Liver biopsy</td>
<td>3</td>
<td>12,100</td>
<td>165.8</td>
</tr>
<tr>
<td>206</td>
<td>68.0</td>
<td>Dental extractions</td>
<td>3</td>
<td>14,500</td>
<td>213.2</td>
</tr>
<tr>
<td>207</td>
<td>68.0</td>
<td>Dental extractions</td>
<td>3</td>
<td>13,000</td>
<td>191.2</td>
</tr>
<tr>
<td>208</td>
<td>80.0</td>
<td>Dental extractions</td>
<td>4</td>
<td>11,340</td>
<td>141.8</td>
</tr>
<tr>
<td>201</td>
<td>95.0</td>
<td>Total knee replacement</td>
<td>10</td>
<td>42,000</td>
<td>442.1</td>
</tr>
<tr>
<td>204</td>
<td>84.0</td>
<td>Revision arthroplasty</td>
<td>7</td>
<td>22,430</td>
<td>267.0</td>
</tr>
<tr>
<td>209</td>
<td>83.3</td>
<td>Manipulation of knee under anaesthesia</td>
<td>6</td>
<td>21,600</td>
<td>259.3</td>
</tr>
<tr>
<td>210</td>
<td>82.7</td>
<td>Revision arthroplasty</td>
<td>8</td>
<td>34,020</td>
<td>411.4</td>
</tr>
<tr>
<td>211</td>
<td>82.7</td>
<td>Revision arthroplasty (2nd stage)</td>
<td>7</td>
<td>29,400</td>
<td>355.5</td>
</tr>
</tbody>
</table>

Adverse events
A total of 20 AEs was reported in 8 procedures by four patients: pyrexia (3); tachycardia (3); decreased Hb (2); incision site complication (2); nausea (1); ear pain (1); vomiting (1); arthralgia (1); joint stiffness (1); anaemia (1); infusion site erythema (1); low temperature (1); catheter related infection (1) and “slight dizziness” (1).

Only one AE (dizziness) was considered related to treatment.

No significant laboratory safety data is apparent. There were no seroconversions.

Assessor’s comments and conclusion
In this study, there were a total of 95 infusions over 10 days (total of 55 exposure days). Six different batches were used from November 2001 to August 2003. The efficacy based on FVIII monitoring and quality of haemostasis was satisfactory. No safety concerns were raised.

The study provides the required data on the effectiveness of Optivate 100 IU/ml powder for solution for injection in the surgical setting. The data provide reassurance that the product is effective in surgery.
IV.2.4 Study 8vWF05
This was an open-label multi-centre (in 5 centres in Poland: Lublin; Krakow, Warsaw, Wroslaw, Poznan) single arm prospective phase III study to investigate the safety and efficacy of Optivate 100 IU/ml powder for solution for injection in children under 6 years of age with severe haemophilia A. The study was conducted between 6/11/2003 and 26/01/2005.

Table 16: Study outline

<table>
<thead>
<tr>
<th>Study aim</th>
<th>Study design</th>
<th>Study arm</th>
<th>Study phase</th>
<th>Patient population</th>
<th>Outcome measure</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>To investigate the safety and efficacy of Optivate 100 IU/ml powder for solution for injection in children under 6 years of age with severe haemophilia A.</td>
<td>Open-label, multi-centre, phase III, single group prospective non-comparative</td>
<td>Optivate was dosed as bolus doses at times 0 and week 1. Following week 0, Optivate was administered for a 6-month period as on-demand or routine prophylactic therapy, as judged by the investigator and patient’s parent/guardian.</td>
<td>20 on-demand prophylaxis</td>
<td>5 years</td>
<td>M = 20, F = 0</td>
<td>Children &lt; 6 years with a diagnosis of severe haemophilia A (basal FVIII activity ≤ 1% at the time of diagnosis)</td>
<td>Children who had history of inhibitors to FVIII (≥ 0.5 BU). The reason for their exclusion was to avoid enrolling patients whose haemophilia was difficult to control and who were likely to withdraw from the study, and who might have been more likely to develop inhibitors again and thus affect the safety profile of the study drug.</td>
</tr>
</tbody>
</table>

Inclusion criteria
Each subject fulfilled the following inclusion criteria:
- Written informed consent provided by a legal representative (parent/guardian);
- Children who were less than 6 years of age at entry;
- Children who had severe haemophilia A (basal FVIII activity ≤ 1% at the time of diagnosis) without inhibitor to FVIII (if screen test was positive then the quantitative value was < 0.5 BU); and
- Children requiring FVIII therapy, which included previously untreated patients (PUPs).

Exclusion criteria
The exclusion criteria were designed to restrict the study patients to 'reasonably healthy haemophiliacs'. Prospective subjects who met any of the following criteria were to be excluded from participation in the study:
- Children who had a history of inhibitors to FVIII (> 0.5 BU). The reason for their exclusion was to avoid enrolling patients whose haemophilia was difficult to control and who were likely to withdraw from the study, and who might have been more likely to develop inhibitors again and therefore affect the safety profile of the study drug.
- Children who had an INR > 1.5. The reason for their exclusion was to avoid enrolling patients with complicating pathology or whose bleeding patterns were determined by factors other than FVIII deficiency/replacement.
Children who had thrombocytopenia (platelets <50 x 10^9/L). The reason for their exclusion was to avoid enrolling patients whose bleeding patterns were determined by factors other than FVIII deficiency/replacement.

Children who had clinically significant renal disease (creatinine >200 μmol/L).

Children who had clinically significant liver disease (ALT levels greater than three times the upper normal limit). The reason for the last two exclusion criteria was to avoid enrolling patients with medical complications.

Children who, in the opinion of the Investigator, were unlikely to comply with the study protocol.

Children who were participating in another study or had taken part in another study within the previous 30 days. The reason for their exclusion was to avoid carry-over of AEs into the current study which could have been due to the previous clinical study drug. Children previously enrolled in a study (within the 30 day period) involving FVIII products and without any ongoing AEs from the previous study, could be considered for early entry to this study, if, in the Investigator’s opinion, it was in the best interest of the child and would allow continuation of treatment.

Children who were not suffering from severe haemophilia A and had a basal FVIII activity of >1% at the time of diagnosis.

**Test product, dose and mode of administration**

Optivate 100 IU/ml powder for solution for injection was supplied in vials containing nominally 500 IU, to be reconstituted with 5 ml of sterilised water for injections. The product was given as an intravenous (IV) bolus dose, administered at a rate of up to 10 ml/min.

**Selection of doses in the study**

During the study the children were treated either with a routine prophylactic dosing regimen agreed by the Investigator and patient’s parent/guardian, or with a dose calculated to alleviate a spontaneous bleed in accordance with the guidelines given in Table 17 (on-demand treatment).

Patients on routine prophylaxis were also treated with a dose of Optivate 100 IU/ml powder for solution for injection calculated to alleviate a bleed in the event of spontaneous breakthrough bleeds. Patients taking Optivate 100 IU/ml powder for solution for injection on demand were also treated with a dose of Optivate 100 IU/ml powder for solution for injection if the patient was planning on taking part in an activity which might precipitate a spontaneous bleed, for example a sporting event, or rehabilitation of a joint affected by a bleed (‘intermittent prophylaxis’). The two management modalities were not randomised.
Table 17: Guidelines for administration of Optivate

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Plasma concentration of FVIII desired in the patient's blood immediately after infusion (IU per 100ml)</th>
<th>Initial dose of OPTIVATE® (IU per kg bodyweight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor spontaneous haemarthrosis, and muscle haematoma</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>Major haemarthrosis and muscle haematoma; haematuria</td>
<td>40 to 50</td>
<td>20 to 25</td>
</tr>
</tbody>
</table>

**Duration of treatment**
All patients were treated for 6 months.

**Reference therapy**
This was a non-comparative study.

**Criteria for evaluation**
The efficacy assessments consisted of evaluating the consumption of FVIII by assessing the number of infusions, dose (IU/kg) administered for each bleed and routine or intermittent prophylactic therapy. The number, type, duration and severity of bleeds were also assessed for all children. The assessment of clinical outcome was conducted by assessing both patient’s (monthly) and clinician’s (3 monthly) response to treatment for the two patient subgroups (prophylactic and on-demand). The safety assessments consisted of the AEs reported and the findings of the viral infection markers, inhibitors, full blood count and routine serum biochemistry monitored in children during the study.

**Statistical methods used**
Patients who had at least one dose of medication were included in the full analysis set. All primary and secondary efficacy variables were analysed using this set. The per-protocol analysis set was also presented. Descriptive statistics (mean, median, standard deviation, 95% confidence limits, range and interquartile range) was calculated for patients receiving Optivate 100 IU/ml powder for solution for injection on prophylaxis, receiving Optivate 100 IU/ml powder for solution for injection on demand and for overall patients; this set excluded patients with at least one major protocol violation.

**Protocol deviations**
Most of deviations were related to assessment visits.

**Results**
The full analysis set included 25 patients, with 5 patients receiving Optivate 100 IU/ml powder for solution for injection prophylactically and 20 patients receiving Optivate 100 IU/ml powder for solution for injection on demand. Two subjects had just passed their sixth birthday at the time of their first dose of Optivate 100 IU/ml powder for solution for injection and hence were excluded from the per-protocol set. All subjects were male Caucasians.
Overall, age ranged from 1.17 to 6.01 years, with a mean of 4.24 years. Twenty-four (96.0%) patients had been treated with FVIII prior to entry; i.e. one patient was a PUP.

Baseline characteristics
Five out of 25 patients (20%) reported at least one previous medical history. Four out of 25 patients (16%) reported at least one ongoing medical condition.

FVIII Therapy taken in the last 12 months prior to entering the study:
Twenty-four (96%) patients had been treated with FVIII prior to entry. There was one (number 544) previously untreated patient, who had not received FVIII before and therefore had no prior FVIII exposure. The maximum period between the previous FVIII treatment and study entry was 61 months, with a mean of 37.1 months. The mean number of exposure days for previous FVIII treatment was 111.5 days. The most common FVIII treatment in the 12 months prior to entry was Monarc-M (Baxter/American Red Cross) used by 20 (80%) patients. Of the 24 patients who had used FVIII, 22 (91.7%) were using it on demand only. One (4.2%) patient was using it prophylactically and one (4.2%) patient had used FVIII both prophylactically and on demand in the past.

FVIII therapy at the time of screening:
Patient number 500 was receiving Hemofil M Czynnik VIII Method M and patient number 546 had received Monarc-M and Immunate. Of the 23 patients reporting, 19 (82.6%) were using Monarc-M (Baxter/American Red Cross). The mean approximate number of bleeds per month for these patients was 2.7 with mean dose per bleed of 22.0 IU/kg. Two (8.0%) patients reported the use of concomitant medication at screening.

Bleed History:
Five (20%) patients had reported a major joint bleed in the six months prior to the entry into the study. The mean number of minor joint bleeds per week during the six months before entering the study for all patients was 0.69, with a median duration per patient of 1.0 hour, one patient reported a maximum duration of 72 hours. The mean FVIII dose per bleed was 17.6 IU/kg. Only two (8%) patients had reported a major intra-muscular bleed in the six months prior to the entry into the study. The mean number of minor intra-muscular bleeds per week during the six months before entering the study for all patients was 0.34, with a mean duration per patient of 1.5 hours. The mean dose per bleed was 11.7 IU/kg. Five (20%) patients had reported a major open bleed in the six months prior to study entry. The mean number of minor open bleeds per week during the six months before entering the study for all patients was 0.20, with a mean duration per patient of 0.28 hours. The mean dose per bleed was 3.00 IU/kg. This value is very low as a majority of bleeds were not treated.

Efficacy
The mean dose per infusion per patient was 29.1 IU/kg (median 27.2 IU/kg) for the prophylactic subgroup and 28.6 IU/kg (median 27.8 IU/kg) for the on-demand subgroup. The mean dose per bleed per patient for the prophylactic subgroup and on-demand subgroup were 33.6 IU/kg and 28.3 IU/kg, respectively.

Table 18 presents summary statistics of the mean dose in IU/Kg by month based on the full analysis set. The data obtained from the per-protocol set were similar, with the statistical conclusions being unaltered.
The mean Optivate 100 IU/ml dose for solution for injection dose per month (IU/kg) was 299.33 IU/kg for patients receiving Optivate 100 IU/ml powder for solution for injection prophylactically, compared to 150.38 IU/kg for patients receiving Optivate 100 IU/ml powder for solution for injection on demand. This comparison between the two subgroups was statistically significant (p= 0.015). There was a statistically significant difference in the Optivate 100 IU/ml powder for solution for injection dosage between the younger (< 4 years) and older patients (> 4 years; p< 0.01) in both subgroups, in terms of dose per infusion per patient. The mean consumption of Optivate 100 IU/ml powder for solution for injection (IU/kg) was higher in the less than 4 years old subgroup of patients; this difference may be attributed to the use of full vials for all children, rather than a medical need for a larger dose. The mean total dose per patient over the whole study period was 1822.1 IU/kg for those receiving Optivate 100 IU/ml powder for solution for injection prophylactically as compared to 933.1 IU/kg for those receiving Optivate 100 IU/ml powder for solution for injection on demand.

The overall mean number of bleeds per patient was 12.3 for the six month study period, as compared to 16.2 bleeds in the six months prior to starting Optivate 100 IU/ml powder for solution for injection at week 0. There was a statistically significant difference (p< 0.05) between the patient subgroups in the number of bleeds per patient: 8.0 bleeds in the prophylactic subgroup as compared to 13.4 bleeds in the on-demand subgroup (for both analyses sets). The centre analysis was statistically significant with the number of bleeds reported being higher in the Warsaw centre (p< 0.01) for both analyses sets. The age subgroup and patient subgroup-by-age interaction were not statistically significant. The prophylactic subgroup required less Optivate 100 IU/ml powder for solution for injection to treat a bleed as compared to the on-demand subgroup: the mean dose per bleed per patient for the prophylactic subgroup and on-demand subgroup was 35.5 IU/kg and 42.1 IU/kg, respectively.

The responses to therapy by both the clinician and the patient (as recorded by the parent/guardian) were graded as ‘excellent’ and ‘very helpful’ in all five patients of the prophylactic subgroup. Responses to spontaneous bleeds were comparable for both subgroups. On 98.4% of the occasions, the patient (as recorded by the parent/guardian) found Optivate 100 IU/ml powder for solution for injection treatment either ‘helpful’ or ‘very helpful’, demonstrating efficient management of spontaneous bleeds.
Safety

The study duration in terms of weeks ranged from 24.9 to 34.1 weeks, with a mean of 26.6 weeks. The overall number of patient-years for the 25 patients who received at least one dose of study medication was 12.7.

Table 19: Spontaneous bleed summary for the children study (8vWF05)

<table>
<thead>
<tr>
<th>Study</th>
<th>Prophylactic use</th>
<th>Spontaneous use</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>$8vWF05$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of children</td>
<td>5</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>Mean exposure period (weeks)</td>
<td>25.9</td>
<td>26.8</td>
<td>26.6</td>
</tr>
<tr>
<td>Total number of bleeds reported</td>
<td>40</td>
<td>267</td>
<td>307</td>
</tr>
<tr>
<td>Average number of bleeds per patient</td>
<td>8.0</td>
<td>13.4</td>
<td>12.3</td>
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<tr>
<td>Duration of bleed (hours)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>7.7</td>
<td>16.3</td>
<td>15.2</td>
</tr>
<tr>
<td>SEM</td>
<td>1.8</td>
<td>1.8</td>
<td>1.6</td>
</tr>
<tr>
<td>Severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>40 (100.0%)</td>
<td>233 (94.8%)</td>
<td>293 (95.4%)</td>
</tr>
<tr>
<td>Major</td>
<td>0</td>
<td>14 (5.2%)</td>
<td>14 (4.6%)</td>
</tr>
<tr>
<td>Not available</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Response assessed by subject</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very helpful</td>
<td>19 (47.5%)</td>
<td>125 (46.8%)</td>
<td>144 (46.9%)</td>
</tr>
<tr>
<td>Helpful</td>
<td>20 (50.0%)</td>
<td>138 (51.7%)</td>
<td>158 (51.5%)</td>
</tr>
<tr>
<td>Helped a little</td>
<td>1 (2.5%)</td>
<td>3 (1.1%)</td>
<td>4 (1.3%)</td>
</tr>
<tr>
<td>Not available</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Response assessed by clinician</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent</td>
<td>21 (22.5%)</td>
<td>124 (46.4%)</td>
<td>145 (47.2%)</td>
</tr>
<tr>
<td>Good</td>
<td>2 (3%)</td>
<td>79 (29.6%)</td>
<td>81 (26.4%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>17 (42.5%)</td>
<td>64 (24.0%)</td>
<td>81 (26.4%)</td>
</tr>
<tr>
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</table>

Overall 23 (92%) subjects reported a total of 101 AEs. A total of 18 out of 20 (90%) patients who received Optivate 100 IU/ml powder for solution for injection on demand reported a total of 87 AEs. All five patients who received Optivate 100 IU/ml powder for solution for injection prophylactically reported a total of 14 AEs. Most AEs were mild (92.1%) and only 4 infusion site reactions and one mild rash in the on-demand subgroup were reported to have a causal relationship to Optivate 100 IU/ml powder for solution for injection administration.
Deaths
There were no deaths reported in this study.

Other serious AEs
Only one serious AE was reported, which was not related to study medication. Patient number 511, aged four years, developed interstitial pneumonia approximately five months after entry into the study. The patient was admitted to hospital and was treated with intravenous antibiotics. The AE lasted for 31 days; the event was classed as an SAE for 13 days. In the opinion of the Investigator, the AE was not related to Optivate 100 IU/ml powder for solution for injection. As it required hospitalisation, it was graded as a serious AE.

Other significant AEs
There were no other significant AEs reported in this study.
Laboratory parameters, inhibitors, viral safety
There were no clinically significant changes in haematology or biochemistry from screening to weeks 13 and 26. No FVIII inhibitor development was observed. The changes in vital signs were not clinically significant. Three of the 25 patients (12%) reported mild infusion site reactions. Safety in terms of viral serology was very satisfactory as all patients were negative for anti-HIV1, anti-HIV2, anti-HCV and anti-HAV (IgM) at week 0 and at the post-study follow-up, except for two patients who turned seropositive to HAV (IgG), as a result of hepatitis A vaccination.

PUPs
There was one previously untreated patient. This patient had a baseline FVIII of 0.01 IU/ml. He received two bolus infusions of Optivate 100 IU/ml powder for solution for injection at week 0 and week 13, at which times his pre-infusion FVIII was reported as 0.07 and 0.08 IU/ml. He did not receive any other infusions throughout the study period. He did not experience any spontaneous bleeds of clinical significance during the study period and had no AEs related to Optivate 100 IU/ml powder for solution for injection, no occurrence of viral transmissions and no development of FVIII inhibitors, at least up to 3 months after his last (second) infusion of Optivate 100 IU/ml powder for solution for injection (end of study).

Assessor’s comments and conclusion
The inclusion/exclusion criteria for 8VWF05 study were satisfactory. The baseline levels of FVIII were satisfactory to the definition of severe haemophilia A for all patients.

The protocol deviation list contains information on patient 520 WRO who has received another FVIII in the last week of the study. This patient has not been excluded from the analysis of the study since he/she did not receive subsequently any dose of Optivate 100 IU/ml powder for solution for injection. This is acceptable.

Seven subjects were administered 97 doses greater than 40 IU/kg (9.63% of the total doses consumed across the whole study) ranging from 40.24 to 58.24 IU/kg. However no safety concerns were identified. The results of the paediatric study 8vWF05 indicate that the mean doses of Optivate 100 IU/ml powder for solution for injection used in the prophylactic and on-demand modalities of treatment correspond to those recommended in the core SPC guide range. There were no cases of inhibitor development.

Lymphocytic interstitial pneumonia has been previously described in patients with haemophilia who were HIV-positive. The HIV test in this patient was negative, which is reassuring. In addition, the applicant has provided sufficient information to conclude that the patient’s interstitial pneumonia was not related to serum sickness or any hypersensitivity reaction.

This study provides the required paediatric data in accordance with the CPMP guideline. Optivate 100 IU/ml powder for solution for injection did not induce any inhibitor formation in the 25 children enrolled.
**IV.2.5 Other surgical procedures with Optivate 100 IU/ml powder for solution for injection**

OSE (report dated 20.02.2006)
This is a named patient scheme but all the patients are part of the long-term follow-up of either the PK or the SE study.

The procedures were orthopaedic (7), dental extractions (3), ENT (1), ocular (1), and removal of Portacath (1). Seventy-five (75) infusions were administered from 10 different batches. The duration of treatment at the hospital ranged from 1 to 10 days. The mean pre-operative bolus dose was 40.1 IU/kg (18.2–88.2) and the mean total dose on the first day was 53.0 IU/kg (20.4–88.2); doses on the subsequent days decreased in most cases. Three patients also received tranexamic acid.

The effect was judged excellent or good in 9/10 cases where no tranexamic was given (missing data in the last case). No unusual blood loss was reported during the operation or in the post-operative period.

Some laboratory variables were measured according to medical need. One patient recorded chronically low haemoglobin after the surgical interventions in the surgery studies (8vWF02 and OSE), and received blood transfusions on four separate procedures. In total, the patient was infused 15 units of blood across the two studies. His anaemia was considered related to his underlying medical conditions. In addition to his haemophilia, he had had hepatitis C attributed to 1983, a hiatus hernia diagnosed in 1994, ulcerative colitis since 1997 and haemorrhoids since 1998.

The same patient was also reported to have raised alanine aminotransferase levels post-operatively in the OSE study, which was considered to be related to the concomitant therapy. During his hospitalisation, this patient was given intensive antibiotic treatment with a variety of antibiotics to control an infection in his knee: vancomycin, ciprofloxacin, gentamicin, teicoplanin and meropenem, all intravenously as well as metronidazole and rifampicin orally. No other AE was reported in the OSE study.

**Assessor’s comment and conclusion**
This retrospective data collection provides supportive information to study 8vWF02 on surgical interventions. No unexpected safety concerns were raised during this long-term follow-up.

**IV.3 Clinical expert report**
The clinical overview is by the Medical Director of BPL. It is an accurate summary of the dossier.

**IV.4 Product particulars**

**IV.4.1 Summary of Product Characteristics**
The statements in the SmPC for FVIII products are governed by the CPMP Core SPC CPMP/BPWG/1619/99.
The SmPC for Optivate 100 IU/ml powder for solution for injection is in line with the Core SPC.

IV.4.2 Patient Information Leaflet
The PIL is satisfactory and consistent with the content of the SmPC.

Results of consultations with target patient groups have been provided and are satisfactory.

IV.4.3 Labelling
Satisfactory from a clinical perspective.

IV.5 Assessors overall comments

Optivate 100 IU/ml powder for solution for injection is a modification of a previous BPL FVIII product; the chief difference being a new viral inactivation step (S-D treatment). This change is welcomed since it should be associated with enhanced patient safety.

The clinical development is in line with the relevant CPMP guideline for a new FVIII plasma-derived product.

The clinical trial data are considered sufficient and adequate in terms of kinetics and efficacy in surgical procedures. The safety data are considered satisfactory in terms of general safety, virology and inhibitor formation.

IV.6 Recommendation

The grant of a marketing authorisation is recommended for this application.

V User consultation

The package leaflet has been evaluated via a user consultation study, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC.

The results show that the package leaflet meets the criteria for readability, as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The benefit/risk assessment is, therefore, considered to be positive.
Annex 2 – Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report
(Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/non approval</th>
<th>Assessment report attached Y/N (version)</th>
</tr>
</thead>
<tbody>
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