Multicentre, Non-controlled, Prospective, Post-Marketing Safety Study Following Long-Term Prophylactic Optivate® Treatment in Subjects with Severe Haemophilia A.

Study Code: 8VWF07
EudraCT Number: 2012-004606-10

Final Version 4
30 November 2015

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PROTOCOL APPROVAL SIGNATURES

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30 November 2015

I have carefully read this protocol and I confirm that it contains all the information necessary to perform the study. This study is to be conducted in accordance with the protocol, ICH GCP and applicable regulatory requirements.

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Information contained within this document will be treated as confidential at all times. It shall be used for the sole information of the Investigator's team. Staff must undertake not to disclose any such information to any person not involved in the study.

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LIST OF ABBREVIATIONS

AE	Adverse Event(s)
ADR	Adverse Drug Reaction
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
APTT	Activated Partial Thromboplastin Time
BPL	Bio Products Laboratory Ltd (The Sponsor)
BU	Bethesda Units
CD4	Cluster of differentiation 4
CHMP	Committee for Medicinal Products for Human Use
CPMP	Committee for Proprietary Medicinal Products
CRA	Clinical Research Associate
CRF	Case Record Form
ED	Exposure day(s)
EMA	European Medicines Agency
EU	European Union
FFP	Fresh-Frozen Plasma
FU	Follow-Up
FVIII	Factor VIII
GCP	Good Clinical Practice
HAV	Hepatitis A Virus
Hb	Haemoglobin
HBV	Hepatitis B Virus
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HEENT	Head, Ears, Eyes, Nose, Throat
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	Identification
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intention to Treat
IU	International Units
kg	Kilograms
Ltd	Limited
MedDRA	Medical Dictionary for Regulatory Authorities
MHRA	Medicines and Healthcare products Regulatory Agency (regulatory authority for the United Kingdom)
min	Minute(s)
mL	Mililitre(s)
mol	Molar
mon	Month(s)
PIS	Patient Information Sheet
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System

SD	Standard Deviation
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
UK	United Kingdom
USA	United States of America
V	Visit
vs.	Versus
wk(s)	Week(s)

1. SYNOPSIS

PROTOCOL NUMBER:	8VWF07
INVESTIGATIONAL MEDICINAL PRODUCT (IMP):	Optivate®
TITLE:	Multicentre, Non-controlled, Prospective, Post-Marketing Safety Study Following Long-Term Prophylactic Optivate® Treatment in Subjects with Severe Haemophilia A.
PHASE:	IV
OBJECTIVES:	Primary objective: To assess post-marketing immunogenicity of Optivate® by monitoring plasma inhibitor levels for at least 100 Exposure Days (EDs) for each subject. Secondary objectives: To assess efficacy and tolerability by monitoring factor VIII (FVIII) recovery and Adverse Events (AEs).
STUDY DESIGN:	A post-marketing, open label, multicentre, prospective safety study in subjects with severe haemophilia A following prophylactic therapy with Optivate®. Subjects will attend a minimum of 5 visits over a period of up to 12 months. A recovery assessment will be conducted at each visit (see Figure 1). **Note:** *All recovery assessments in the study will only be conducted after a 3 day washout period and when the subject is not actively bleeding. If these criteria are not been met, the recovery assessment will be re-scheduled.* ***Screening Visit*** Subjects will attend the clinic for Screening within 4 weeks before the Baseline Visit (V1). A brief physical and medical examination will be performed and the subject's medical history recorded (including gene defect, family history of haemophilia, bleed history, ethnicity, history of inhibitors and concurrent diseases). Also blood samples to check the subject's CD4 (cluster differentiation 4) count and Human Immunodeficiency Virus (HIV) viral status will be collected. Following a 3 day washout period, eligible subjects will provide a blood sample to test for FVIII inhibitors (pre-bolus only).

Subjects will also undergo a recovery assessment at this visit using the subject's current FVIII concentrate (30 IU/kg dose). Blood samples will be collected at the following timepoints:

- pre-dose (if not already collected)
- 15 minutes post-infusion (±5 minutes [mins])
- 30 minutes post-infusion (±5 mins)
- 1 hour post-infusion (±10 mins)

After the end of the Screening Visit subjects will record any medication taken, AEs and bleeds at home using the study diary. Subjects will continue taking their current FVIII between Screening and their Baseline Visit (V1).

Visit 1(Baseline)

At the Baseline Visit (V1) after a 3 day washout period, blood samples for viral serology, FVIII inhibitor and long-term archiving (1 mL serum) will be collected. The first dose of Optivate® (30 IU/kg) will then be administered. Blood samples for FVIII:C analysis will be collected at identical timepoints as for the current FVIII recovery.

After the Baseline Visit, subjects will commence home therapy with Optivate® at a prophylactic dose of 20-40 IU/kg three times a week and record Optivate® usage, AEs and bleeds in the study diary. The subject and clinician will assess the severity of any bleed and the effectiveness of Optivate® in treating the bleed.

Visit 2

After approximately 4 weeks, when an estimated 10 to 15 EDs* have been reached, subjects will return for Visit 2. An inhibitor test (pre-bolus) and Optivate® recovery assessment (at identical timepoints and dose as for current FVIII recovery) and inhibitor test (pre-bolus) will be conducted. Subjects then continue on prophylactic Optivate® home therapy (20-40 IU/kg x 3 weekly) and using the study diary as before.

Visit 3

This is scheduled for three months after Visit 2, when an estimated 50 to 75 EDs* would have been reached. An Optivate® recovery assessment (at the same timepoints and dose as at current FVIII recovery) and inhibitor test (pre-bolus) will be conducted. Subjects will then continue on prophylaxis treatment with Optivate® (20-40 IU/kg x 3 weekly) and continue to complete their diary as previously.

Visit 4

This final visit to the site will be scheduled when the subject has had at least 100 EDs*, this is estimated to be between 9 to 12 months (approximately 39 to 52 weeks) after the first dose of Optivate®. A short medical examination will be conducted and blood samples for viral safety, inhibitor assessment and long-term archiving (1 mL serum) will be taken. The final Optivate® recovery will be conducted (at the same dose and timepoints as the current FVIII recovery) and the subject will then be discharged from the study.

*If the minimum number of EDs has not been reached for visits V2, V3 or V4 then the respective visit will be postponed until the minimum number of EDs has been reached.

Safety Follow-Up

This will be conducted by telephone 28 days after the last Optivate® infusion to allow follow-up of any AEs.

NUMBER OF SUBJECTS:

Up to 12 subjects will be enrolled to achieve a minimum of 10 evaluable subjects. If more than two subjects withdraw prior to reaching 100 EDs then subjects will be replaced to ensure 10 evaluable subjects have had at least 100 EDs.

The study will be completed in 4 years. It is planned that all subjects will be recruited within Germany, however if suitable subjects are not identified within the recruitment period, the study may be extended into other countries.

STOPPING RULE(S) SPECIFIC TO THIS STUDY

The study will be terminated when a minimum of 10 evaluable subjects have each experienced at least 100 EDs. End of study is when FUP visit has been completed from the 10th evaluable subject.

Subjects may withdraw from the study at any time or may be withdrawn by the Investigator. Reasons for withdrawal include therapeutic intervention prohibited by the protocol *eg* requirement for FVIII-containing products other than Optivate®, or occurrence of an AE which in the Investigator's opinion is not compatible with the subject's continued participation in the study.

TREATMENT WITH OPTIVATE®:

At Baseline Visit (V1), eligible subjects will receive a bolus dose of Optivate® (30 IU/kg) for recovery assessments. Bolus doses (30 IU/kg) will also be administered at V2, V3, and V4.

Following V1, subjects will start home therapy using Optivate® prophylactically at a dose between 20-40 IU/kg administered three times a week for at least 100 EDs.

As a part of home therapy, subjects will also administer Optivate® for preventative use (prior to physiotherapy or increased physical activity) will be 20-40 IU/kg. Treatment of break-through bleeds will be at a dose agreed with the Investigator and in accordance

with the Summary of Product Characteristics (SmPC)[1] for Optivate®. Excessive bleeding may require treatment at the Investigational site.

If the subject requires surgery this can be conducted under the cover of Optivate®, using doses as recommended in the SmPC[1].

All doses will be to the nearest 1 mL, except for the bolus doses at the Baseline Visit (V1), Visit 2 (V2), Visit 3 (V3) and End-of-Study Visit (V4) which will be to the nearest 0.1 mL.

STUDY DURATION:

The duration of the study for an individual subject, including screening (4 weeks), is estimated to be no longer than 60 weeks. The study will be stopped when 10 evaluable subjects have each had at least 100 EDs. Therefore this may mean that the last two subjects enrolled may receive a shorter treatment period.

STUDY POPULATION

Subject Inclusion Criteria

- Written informed consent or, if less than 18 years of age written assent (where possible) and their parent/guardian's has given written informed consent.
- Severe haemophilia A (< 1% FVIII:C). Subjects suffering from severe haemophilia A (< 2%) may be enrolled, but only after approval by BPL. Subjects with a Factor VIII of < 2% may not constitute more than 50% of the total patient population. A separate statistical evaluation will be conducted for the < 1% and < 2% populations. Basal FVIII level taken from subject's lowest level recorded or the level measured at screening, whichever is lower.
- Previously Treated Patients (PTPs) with > 150 exposure days on prior Factor VIII therapy (of which at least the last 50 EDs or 2 years treatment can be confirmed by way of subject records).
- Immunocompetent with CD4 count > 200 /µL (central lab).
- HIV negative or a viral load < 200 particles /µL (central lab).

STUDY POPULATION:

Exclusion Criteria

- History of inhibitor development to FVIII or a positive result on the Nijmegen-Bethesda at screening (quantitative result of ≥ 0.6 Bethesda Units [BU]) prior to the administration of Optivate®.
- Known or suspected hypersensitivity to the Investigational Medicinal Product (IMP) or its excipients.
- Clinically significant i.e. symptomatic liver disease and/or (historical, within the last 12 months, serum Alanine Aminotransferase [ALT] levels greater than three times the upper limit of the normal range), symptomatic renal disease and/or (historical, within the last 12 months, serum creatinine > 200μmol/L), or coagulopathy other than haemophilia A.
- History of unreliability or non-cooperation (including not being able to complete the study diary).
- Participating in, or have taken part in another trial within the last 30 days.

PRIMARY EFFICACY ENDPOINT:

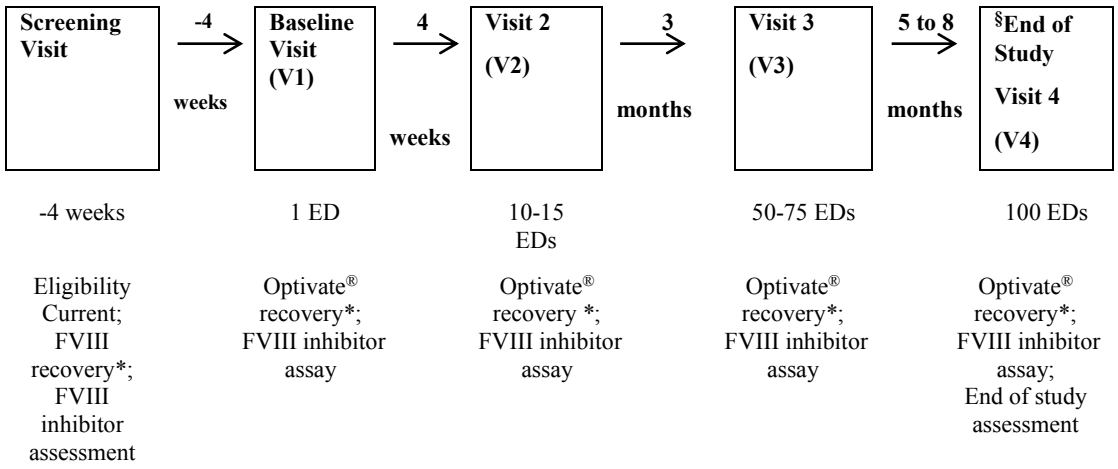
- Immunogenicity of Optivate® by monitoring plasma inhibitor level for at least 100 EDs for each subject.

SECONDARY EFFICACY ENDPOINTS:

- Recovery with current FVIII (Screening Visit) versus (vs.) 1st dose with Optivate® (V1).
- Recovery at 1 ED (V1), 10-15 EDs (V2), 50-75 ED (V3) and 100 EDs (V4).
- Number of break-through bleeds including severity, duration, location and cause.
- Clinician's judgement of break-through bleed treatment outcome (excellent, good, moderate, poor).
- Subject's judgement of break-through bleed treatment outcome (very helpful, helpful, helped a little, did not help).
- Number of exposure days for each subject and per month/subject, per year/subject and overall.
- Total dose in IU/kg of Optivate® and average dose per infusion for prophylactic use, to treat a bleed, any additional preventative use and overall use; all analysed on a per subject basis.
- Total number of infusions for prophylactic use, to treat a bleed, any additional preventative use and overall use; all analysed on a per subject basis.
- Mean dose in IU/kg of Optivate® per subject/month and per subject/year for prophylactic use, to treat a bleed, any additional preventative use and overall use; all analysed on a per subject basis.
- Mean number of infusions per subject/month and per subject/year for prophylactic use, to treat a bleed, any additional preventative use and overall use; all analysed on a per subject basis.

SAFETY ENDPOINTS:	Viral serology, FVIII inhibitor (assessed as a primary efficacy endpoint), physical/medical examinations. Archive samples (1 mL serum) will be collected before first dose of Optivate® (V1) and at the End-of-Study Visit (V4). Also the number of AEs and Serious Adverse Drug Reactions as defined by ICH. The following medical events will automatically be considered as serious. • Anaphylaxis or anaphylactoid reaction • Myocardial infarction • Stroke • Pulmonary embolism • Infection with any blood borne virus • Any transmissible spongiform encephalopathy • Development of inhibitors to Optivate®

Figure 1 Study visit flowchart



*recovery assessments will only be conducted after a 3 day wash-out period and if the subject is not actively bleeding
ED= exposure days
§ 28 days after the last infusion of Optivate® a safety Follow-Up will be conducted via telephone.

This study will be conducted in compliance with the protocol Europeon Union (EU) Clinical Trial Directives 2001/20/EC and 2005/28/EC and applicable local regulatory guidelines.

2. INTRODUCTION

Haemophilia A is a sex-linked recessive disorder of haemostasis caused by a deficiency of factor VIII (FVIII), which occurs almost exclusively in males. The disorder is characterised by bleeding episodes, either spontaneous or resulting from trauma or surgery. The diagnosis of haemophilia A is made on the basis of family history, bleeding history and specific assays for FVIII. The condition may be severe, moderate or mild, depending on the basal level of FVIII.

Treatment of haemophilia A has progressed from the transfusion of fresh-frozen plasma (FFP) and cryoprecipitate to the use of lyophilised FVIII concentrates (*eg* 8Y®). Bio Products Laboratory Limited (BPL) has manufactured 8Y® since 1985 and this has been successfully used to treat both haemophilia A and von Willebrand patients with a very low incidence of viral transmission, inhibitor development or immune disturbances[2,3,4]. BPL has now successfully developed Optivate®, a high purity development of 8Y®. Optivate® is a product with both improved specific activity and two virus inactivation steps: well-established solvent/detergent step to minimise the risk of transmission of enveloped viruses and a terminal heat-treatment step (used in 8Y® and other BPL products for over 15 years) which is acknowledged to be highly effective against a broad range of viruses. This terminal treatment step involves heating the freeze-dried FVIII concentrate in the final container at 80°C for 72 hours[5,6]. For both Optivate® and 8Y® plasma is sourced from screened donors in the United States of America (USA).

Laboratory data suggest that the additional manufacturing steps used to produce Optivate®, do not reduce the efficacy of Optivate® compared with 8Y®.

Summary of Clinical Studies with Optivate®

The following clinical trials have been conducted with Optivate®:

- Pharmacokinetic study (8VWFPK): 15 patients with haemophilia A completed the study[7,8].
- Safety and efficacy study (8VWFSE): 55 patients with haemophilia A completed the study[7,8].
- Bolus dose surgery study (8VWF02): 10 procedures in six patients with haemophilia A were conducted[9]. In addition, further experience of Optivate® in surgery has been obtained from 10 patients undergoing 13 operations while participating in the 8VWFPK and 8VWFSE studies (see above).
- Study in children under 6 years old (8VWF05): 25 children with haemophilia A completed the study[10].

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The clinical data collected from the above studies showed that Optivate® is a safe, efficacious treatment for haemophilia A. BPL obtained a United Kingdom (UK) marketing licence for Optivate® in 2004 for the treatment of haemophilia A in adults and children (UK Product Licence 08801/0051) and since then has obtained marketing licences in several other countries.

Currently the most significant complication in haemophilia treatment is the development of inhibitors[11]. Therefore the Committee for Medicinal Products for Human Use (CHMP) require a post-marketing follow-up study to assess wider exposure to the product[12]. In the 8VWFSE and 8VWFPK studies BPL included an 18 month follow-up period to assess post-marketing safety of Optivate®: during this period a total of 8,255 infusions over 8,157 exposure days were administered across the two studies. These two studies provided data on 130 'patient-years' with Optivate® in PTPs: there were no cases of inhibitor development or viral transmission[7,8]. In the 8VWF05 study, data on over 12 'patient-years' with Optivate® in children with haemophilia A was obtained, again with no cases of inhibitor development or viral transmission[10]. Since the marketing authorisation in the UK and up until November 2012, approximately 264 million IU of Optivate® has been sold worldwide. To date only 12 Adverse Events (AEs) have been reported with no reports of inhibitor formation.

For additional information, please see the SmPC[1].

Current protocol

The current protocol (8VWF07) is being conducted to provide additional post-marketing safety data in Germany (as part of the German marketing authorisation approval). For this study the German regulators agreed a sample size of 10 evaluable subjects. Therefore up to 12 subjects will be enrolled to ensure sufficient data for 10 evaluable subjects.

3. STUDY OBJECTIVES

Primary objective:
To assess post-marketing immunogenicity of Optivate® by monitoring plasma inhibitor levels for at least 100 Exposure Days (EDs) for each subject.

Secondary objectives:
To assess efficacy and tolerability by monitoring FVIII recovery and adverse events.

4. STUDY DESIGN

4.1 Study Design

This is a multicentre, non-controlled, prospective, post-marketing safety study following long-term prophylactic Optivate® treatment in subjects with severe haemophilia A.

At Baseline Visit (V1), eligible subjects will receive a bolus dose of Optivate® (30 IU/kg) for recovery assessments. Bolus doses (30 IU/kg) will also be administered at V2, V3, and V4. Following V1, subjects will start home therapy using Optivate® prophylactically at a dose between 20-40 IU/kg administered three times a week for at least a 100 EDs.

It is intended that a maximum of 12 subjects will be enrolled in order to achieve a minimum of 10 evaluable subjects. If more than 2 subjects withdraw before they have reached 100 EDs at any time during the study, then a suitable number of subjects will be replaced to ensure that 100 ED data is collected for 10 evaluable subjects. Except for the reduced sample size, the study is designed in accordance with CHMP guidelines[12].

Visits will be scheduled according to the estimated number of EDs with Optivate®; if the minimum EDs for a particular visit has not been reached then the visit must be re-scheduled.
All recovery assessments will only be conducted after a 3 day washout period and when a subject is not actively bleeding.

Primary and secondary endpoints are listed in Sections 8.1.1 and 8.1.2.

4.2 Study Plan

Subjects will undergo the visit schedule as shown in Section 4.2.1. The trial procedures for each visit are detailed in Section 7. A recovery assessment will be conducted at each visit, after a 3 day washout period.

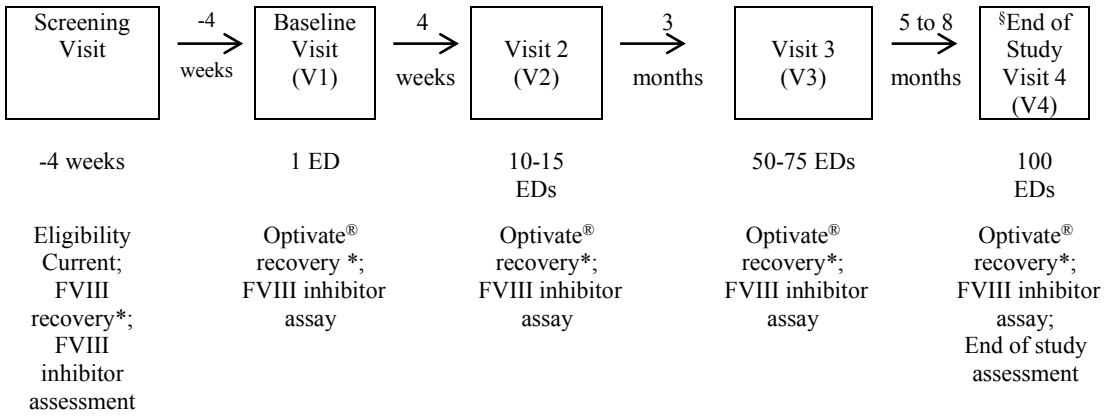
The study will be stopped once 10 evaluable subjects have had at least 100 EDs with Optivate®, which is estimated to be between 9 to 12 months after the first dose of Optivate®. Once 100 ED data on 10 evaluable subjects has been confirmed the study will be stopped and all remaining subjects will have an End-of-Study visit conducted i.e end of study is when FUP visit has been completed from the 10th evaluable subject.

The duration of the study for each subject is estimated to be no longer than 60 weeks in total, comprising of a variable screening period (approximately 4 weeks) and a treatment period of up to 12 months (52 weeks) and a telephone Safety Follow-up (FU) which will be conducted 28 days after the last infusion of Optivate® .

4.2.1 Scheduled Visits

Following enrolment, the subject will attend the hospital for a minimum of 5 study visits, as presented in Figure 1 below.

Figure 1 Study visit flowchart



*recovery assessments will only be conducted after a 3 day wash-out period and if the subject is not actively bleeding
ED= exposure days
§ 28 days after the last infusion of Optivate® a safety Follow-Up contact will be conducted via telephone

If the minimum number of exposure days (ED) has not been reached for V2, V3 or V4, then the site staff will contact the subject to re-schedule the visit to when this is expected to be reached.

All scheduled visits will take place at the Investigational site (study centre). Between visits doses will be administered as per local practice, which could be at home by the subject, or for a young child by the parent/guardian (this is applicable throughout the protocol), or at the local clinic (home therapy). For the purposes of this study all will be considered home therapy. However, subjects will be instructed to contact the site staff if they have an emergency bleed or are concerned about excessive bleeding. If considered necessary by the site staff, the subject will be required to attend the hospital (unscheduled visit). If a positive inhibitor result is suspected then a recovery assessment will also be conducted.

4.2.2 Unscheduled Visits

Unscheduled visits may take place at any time during the study for any of the following reasons:

a) If the subject is concerned about their treatment, or excessive bleeding or an emergency bleed (see Section 7.7.1).
b) If the subject needs additional Optivate® supplies.
c) For collection of repeat blood samples, or for clinical observation or advice (see Section 7.7.2).
d) For collection of additional FVIII inhibitor samples, if an inhibitor is suspected (see Section 7.7.2).
e) Subjects may also be asked to return to the clinic at any time as part of routine patient care, if considered appropriate by the Investigator (see Section 7.7.2).

During the above visits and if time permits, the site staff may review any outstanding data from the study diary *eg* AEs and resolve any queries with the subject.

4.3 Duration of Treatment

Subjects will participate in the study until they have experienced at least 100 EDs (anticipated to be no more than 12 months treatment). The duration of the study for each subject is estimated to be no longer than 60 weeks in total, comprising of a variable screening period (approximately 4 weeks) and a treatment period of up to 12 months (52 weeks) and a telephone Safety Follow-Up (FU) which will be conducted 28 days after the last infusion of Optivate® .

All subjects will attend an End-of-Study Visit (V4); this will be the subject's last visit to the study centre.

5. STUDY POPULATION

5.1 Subject Numbers

A total of 12 subjects will be enrolled in order to achieve at least 10 evaluable subjects (as agreed with the German regulatory authority). If more than 2 subjects withdraw before they have reached 100 EDs, then a suitable number of subjects will be replaced to ensure that data is collected for 10 evaluable subjects for at least 100 ED each.

Subjects will be identified by a unique five-digit number as follows. Each site will be allocated a two-digit site number (*eg* Site 01, *etc*). Once approved by BPL, each subject will be allocated a three-digit subject number (*eg* 001) at the Screening Visit. Each subject identity will consist of a unique site and subject number (*eg* 01001). Once a number has been assigned, it may not be assigned to another subject. All subjects will be issued with a subject identification (ID) card to explain to other medical professionals that the subject is enrolled in this study. The ID card will also detail the study title, study code and agreed dose of Optivate® to be administered for routine prophylaxis, preventative use and to treat a bleed. Subjects will be instructed to carry the ID card with them at all times during the study.

Subjects who fail screening may be recruited into the study if they meet all the inclusion and exclusion criteria on re-screening (see Section 5.2 and 5.3). All screening assessments (see Section 7.1) are to be repeated, with the exception of medical history, which should be updated since the last Screening Visit. If a subject is re-screened a new subject number will be issued.

5.2 Inclusion Criteria

All these criteria must be met for the subjects to be eligible:

- Written informed consent or, in the case of children and adolescents (less than 18 years of age) have given written assent (where possible) and whose parent/guardian has given written informed consent.
- Severe haemophilia A (< 1% FVIII:C). Subjects suffering from severe haemophilia A (< 2%) may be enrolled, but only after approval by BPL. Subjects with a FVII < 2% may not constitute more than 50% of the total patient population. A separate statistical evaluation will be conducted for the < 1% and < 2% populations. Basal FVIII level taken from subject's lowest level recorded, or the level measured at screening, whichever is lower.

- Previously Treated Patients (PTPs) with > 150 exposure days on prior FVIII therapy (of which at least the last 50 EDs or 2 years treatment can be confirmed by way of subject records).
- Immunocompetent subjects with CD4 (cluster differentiation 4) count > 200 /µL.
- Human Immunodeficiency Virus (HIV) negative subjects or a viral load < 200 particles /µL.

5.3 Exclusion Criteria

The presence of any one of these criteria makes the subject ineligible:

- A history of inhibitor development to factor VIII or a positive result on the Nijmegen-Bethesda at screening (quantitative result of ≥ 0.6 Bethesda Units [BU]) prior to administering Optivate®.
- Known or suspected hypersensitivity to the Investigational Medicinal Product (IMP) or its excipients.
- Clinically significant:
    - Symptomatic liver disease and/or (historical, within the last 12 months, serum Alanine Aminotransferase [ALT] levels greater than three times the upper limit of the normal range)
    - Symptomatic renal disease and/or (historical, within the last 12 months, serum creatinine > 200µmol/L), or
    - other coagulopathy other than haemophilia A.
- A history of unreliability or non-cooperation.
- Participating or have taken part in another trial within the last 30 days.

6 INVESTIGATIONAL MEDICINAL PRODUCT

At Baseline Visit (V1), eligible subjects will receive a bolus dose of Optivate® (30 IU/kg) for recovery assessments. Bolus doses (30 IU/kg) will also be administered at V2, V3, and V4.

Following V1, subjects will start home therapy using Optivate® prophylactically at a dose between 20-40 IU/kg administered three times a week for at least 100 EDs.

As a part of home therapy, subjects will also administer Optivate® for preventative use (prior to physiotherapy or increased physical activity) or to treat break through bleeds. This will be at a dose agreed with the Investigator and in accordance with the Summary of Product Characteristics (SmPC)[1] for Optivate®. Excessive bleeding may require treatment at the Investigational site.

If the subject requires surgery this can be conducted under the cover of Optivate®, using doses as recommended in the SmPC[1], also see Section 6.2.3.

All doses will be to the nearest 1 mL, except for the bolus doses at the Baseline Visit (V1), Visit 2 (V2), Visit 3 (V3) and End of Study Visit (V4) which will be to the nearest 0.1 mL.

6.1 Product Presentation

Optivate® will be supplied by BPL in vials containing nominal unitages of 500 IU which will be reconstituted in 5 mL of water for injections. The vials will be labelled with the batch number, nominal unitage, , expiry date and study code. The vial cartons will have space to enter the site details and subject number. Actual vial content in IU will be specified either on the corresponding Certificate of Analysis for each batch, or on the vial label, which should be used to calculate dosage.

For information regarding reconstitution and administration, please see Appendix V.

6.2 Product Administration

For the purposes of the trial, 'home therapy' will include any therapy administered to a subject at a local clinic or their home, but which is not the Investigational site (study centre).

Subjects will receive their first dose of Optivate® (30 IU/kg) at the Investigational site at V1 (Baseline Visit). The subjects will then be provided with Optivate® for administration at home or treatment at their local clinic at a dose of 20-40 IU/kg three times a week. The subject will undergo treatment for at least 100 EDs. The dose range is as per the SmPC[1] and the frequency of three times a week has been selected to ensure subjects reach 100 EDs within the 12 month treatment period.

Optivate® is given by intravenous infusion. Doses will be calculated using the actual vial content for each batch and not the nominal unitage. Doses administered before recovery assessments will be measured precisely to the nearest 0.1 mL. All other doses will be rounded to the nearest 1 mL. Any unused reconstituted product should be discarded.

For each subject, sufficient product of a single batch of Optivate® should be reserved wherever possible to ensure that all infusions are carried out using the same batch of Optivate®.

Actual dose will be calculated based on the actual Optivate® content for the batch, according to the potency described on the Certificate of Analysis or printed on the vial label. . The following details will be recorded in the CRF for Optivate® administered at recovery assessment:

- batch number
- actual Optivate® content per vial (IU)
- standard dose (IU/kg) of 30 IU/kg
- calculated dose (IU) *ie* based on the subject's weight
- calculated volume to be infused (mL)
- actual volume infused (nearest 0.1 mL)
- actual dose given (IU) derived/manually entered .

6.2.1 Bolus dose at Recovery assessment

Optivate® recovery assessments will be conducted at V1, V2, V3 and V4. The bolus doses administered at these visits will be 30 IU/kg of Optivate®. All details of the dose calculation and doses administered will be recorded in the CRF. The dose administered will be based on the subject's weight at that visit. Unused reconstituted product should be discarded according to local regulations. Sites must retain the empty cartons for all used vials, so the CRA can complete drug accountability.

6.2.2 Home Therapy

For the purposes of this study all Optivate® doses administered by the subject or at a local clinic (other than at the study centre) will be considered home therapy. Where doses are administered at a local clinic the study centre staff needs to ensure that the local clinic is provided with a copy of the guidelines in Appendix IV.

After the first dose of Optivate®, subjects will be provided with sufficient Optivate® for routine prophylactic treatment and to treat any spontaneous bleeds at home between study visits.

The subjects must be trained in product administration by the study centre staff, with the date of training recorded in the hospital notes. Instructions to the subject as to the exact volume to be administered will be provided by the study centre staff and the agreed doses for routine prophylaxis, preventative use and to treat a bleed will be recorded in the subject's study ID card or equivalent. Prior to issuing the subject with Optivate®, the Investigational site staff must explain

the importance of administering the exact volume of reconstituted product (calculated dose rounded to the nearest 1 mL).

NOTE: This may be different to the subject's prior experience of a home therapy treatment regimen.

Subjects will also be instructed in the secure storage of unused vials in an appropriate location and temperature, according to the instructions on the carton (see Section 6.3).

To allow the site staff to complete drug accountability subjects will be reminded to count the number of unused vials at home to inform the site staff and to bring the empty cartons of used vials with them at each visit (also see Section 6.5). Subjects will dispose of used vials safely and immediately after use, as they may contain small amounts of reconstituted product.

6.2.2.1 Routine Prophylaxis

To ensure 100 EDs for at least 10 evaluable subjects, all subjects will be dosed prophylactically, with a routine dose between 20-40 IU/kg (agreed by the Investigator) administered three times a week. The Investigator will continually monitor the prophylactic dose set for each subject. If the prophylactic regime needs to be adjusted to twice weekly this will be discussed with BPL and agreed on a case by case basis.

6.2.2.2 Dosage to Treat Break Through Bleeds

Between visits the subjects will also treat bleeds at home. Before they are supplied with Optivate® the site staff will ensure that each subject is aware of what dose they need to administer to treat a bleed. Subjects will need to assign the severity of each bleed (major, minor or emergency) in the study diary, where a major bleed is defined as a bleed that unacceptably restricts the patient's day-to-day life. If there is excessive bleeding or an emergency bleeds occurs, the study site staff should be contacted as soon as possible.

The doses for a bleed will be agreed with the Investigator and in accordance with the SmPC for Optivate®[1] and the guidelines given in Table 1:

Table 1: Doses to treat a bleed

Degree of haemorrhage	Factor VIII level required (%) (IU/dL)	~Estimated Optivate® dose in IU/kg	Frequency of doses (hours)/ Duration of therapy (days)
Early haemarthrosis, muscle bleeding or oral bleeding	20-40	8-15	Repeat every 12 to 24 hours . At least 1 day, until the bleeding episode as indicated by pain is resolved or healing is achieved.
More extensive haemarthrosis, muscle bleeding or haematoma.	30-60	12-23	Repeat infusion every 12 to 24 hours for 3-4 days or more until pain and acute disability are resolved.
Life threatening haemorrhages	60-100	23-37	Repeat infusion every 8 to 24 hours until threat resolved.

~Calculated using the SmPC[1] mean recovery value for Optivate® of 2.7 IU/dL per IU/kg.

The Investigator will continually review the dose set to treat a bleed for each subject and if needed adjust this accordingly.

If the bleed happens on the prophylaxis dosing day, then depending on the severity of the bleed, either the prescribed prophylaxis dose or the prescribed bleed dose may be administered based on Investigator decision and patient's best interest.

6.2.2.3 Preventative Therapy

In addition to their routine prophylaxis, some subjects may require an additional dose of Optivate® for a short period; for example, in anticipation of increased physical activity, or during rehabilitation of a joint following a bleed. This use of Optivate® will be recorded as 'preventative therapy'. A single dose of 20-40 IU/kg should be administered. Unlike doses to treat a bleed, the dose for preventative treatment will remain fixed for an individual subject between 20-40 IU/kg throughout the study for all subjects.

If the preventative dosing falls on the prophylaxis dosing day, either the prescribed prophylaxis dose or the prescribed preventative dose may be administered based on Investigator decision and patient's best interest.

6.2.3 Therapy During Surgery

If the subject requires surgery, this can be conducted under the cover of Optivate®. In such cases, doses should be administered as detailed in the SmPC[1] and guidelines given Table 2:

Table 2: Doses during surgery

Type of surgical procedure	Factor VIII level required (%) (IU/dL)	~Estimated Optivate® dose in IU/kg	Frequency of doses (hours)/ Duration of therapy (days)
Minor surgery Including tooth extraction	30-60	12-23	Every 24 hours, at least 1 day, until healing is achieved.
Major surgery	80-100 (pre- and postoperative)	30-37	Repeat infusion every 8 to 24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a factor VIII activity of 30% to 60% (IU/dL).

~Calculated using the SmPC[1] mean recovery value for Optivate® of 2.7 IU/dL per IU/kg.

Data on the type of surgery, if it is planned or an emergency surgery, any complications, mode of administration and the amount of Optivate® used will be recorded in the CRF. The use of antifibrinolytic agents in the study are only permitted during surgery (see Section 7.12). If antifibrinolytic agents need to be administered during the surgery *eg* during dental surgery, the surgery exposure days SHOULD NOT be included in the Optivate® ED calculations. In such cases both the CRA and the Sponsor need to be notified that an antifibrinolytic agent has been administered (also see Section 7.12).

If an AEs is considered to be related to surgery or a complication of surgery this will be specified on the AE the form. If the AE meets the definitions of a Serious Adverse Event (see Appendix I) this will be reported as a SAE. Any excessive bleeding as a result of the surgery will be recorded as an AE.

6.3 Storage and Expiry

The product will be stored in its carton between 2°C and 25°C (36-77°F). An expiry date is printed on the label. The product must not be used after the expiry date. Study medication and diluents must be stored securely.

6.4 Concurrent Medication

FVIII-containing products apart from BPL's Optivate® must not be taken after the Baseline Visit (V1).

The use of antifibrinolytics *eg* tranexamic acid is prohibited during the study (except in the case of surgery, see Section 6.2.3 and 7.12).

Use of all non-study medication, excluding herbal or homeopathic remedies, will be documented in the CRF and the subject diaries. The following information must be entered:

- The start date of treatment.
- The reason for treatment.
- The generic name of the drug and its presentation. In the case of combined products where 'co-generic' names are not available, a trade name should be provided. Subjects may choose to use trade names of the drug in the study diary, which is acceptable. The site staff will need to check that the drug names are spelt correctly and if needed amended by the subject.
- The total dose given.
- The treatment stop date.

6.5 Drug Accountability

The Investigator is responsible for ensuring that a record is maintained for every vial provided for the study. In this study only vials with a nominal unitage of 500 IU will be used. **Accounts must be kept of all shipments and for each subject, which include the number of vials dispensed, used and returned unused, in order to demonstrate full drug accountability.** Used and partly used vials will be disposed of in a safe manner, *eg* a box specially designed to dispose of sharp objects or needles, immediately to avoid accidental administration of previously reconstituted Optivate®. The cartons will therefore be used in place of the discarded used vials for drug accountability purposes.

The staff at the study centre will confirm receipt of the study supplies, indicating dates, batch numbers and quantities of all study supplies received from the Sponsor / Central Drug Distributor. Records will be kept of medication issued/administered to subjects and returned to the centre unused or damaged, as well as amounts remaining at the study conclusion. Before vials are issued to the subject, the site staff will ensure that the subject number is clearly displayed on the box. Upon completion of the study the study monitor or lead CRA will arrange for the collection of unused supplies for return to the Sponsor/Central Drug Distributor.

The following records will therefore need to be maintained to provide complete accountability:

- Despatch notes or invoice slips.
- Receipt forms.
- Dispensing log/returns log.
- Returns to the Sponsor / Central Drug Distributor.

It is essential that all study product administered/issued to the subject is recorded in the subject's hospital notes including amount administered or issued for home use and the batch number. If the amount of Optivate® dispensed to the subject is not sufficient, the subject will return to the hospital for a further supply of Optivate®. **No subject should be dispensed with more than one batch of study product, or have more than one batch of study product at home.** If insufficient product of a single batch is available until the next visit, or the product will expire before the next visit, the subject must attend the clinic for more supplies (see Section 7.7.2).

The subject will update the site staff on the number of unused study product at home and return cartons of the used vials to the hospital at each scheduled visit, for an accountability check. If the site has asked the subject to bring in the unused study drug to resolve any drug accountability queries then this may be re-dispensed to the same subject.

If a clinic local to the subject's home is to administer Optivate® in between the scheduled visits, the subject should store the Optivate® at home and take it to the clinic for dosing. It is the responsibility of the Investigational site to ensure subjects routinely have access to study treatment.

The product provided for the study must be used solely as indicated in the protocol and must never be used for subjects not participating in the study.

6.6 Treatment Available After the Study

Following the study, subjects may continue with Optivate® treatment using commercially available vials, as this product is licenced in Germany. Alternatively subjects may return to their previous FVIII therapy.

Optivate® supplies issued to the subject after study completion will need to be purchased by the Investigational site, as per local procedure.

6.7 Summary of Optivate® Dosing Schedule

Table 3: Summary of dosing schedule per timepoint

Timepoint	Dosage	Frequency
V1, V2, V3 and V4	30 IU/Kg	Single bolus dose
Routine prophylactically	20-40 IU/kg	3 x week
Preventative	20-40 IU/kg	Single bolus dose
To treat a bleed	8-15 IU/kg for early haemarthrosis, muscle bleeding or oral bleeding 12-23 IU/kg for more extensive haemarthrosis, muscle bleeding or haematoma. 23-37 IU/kg for life threatening haemorrhages Also see Section 6.2.2.2 and SmPC[1]	More than one dose can be administered if a bleed is not controlled. In the case of excessive bleeding or an emergency bleed the Investigational site should be contacted
Surgery	12-23 IU/kg for minor surgery 30-37 IU/kg for major surgery Also see Section 6.2.3 and SmPC[1]	

7 TRIAL PROCEDURES

A detailed flowchart showing assessments to be performed is located in Appendix VI.

7.1 Screening Visit: up to Weeks (wks.) -4

Written information and an oral explanation of the study covering its nature, purpose, risks and requirements will be given to the subjects. In the case of subjects under the age of 18 years, assent will be obtained and written consent will be obtained from the subject's parent(s)/guardian(s). Consent and assent will be conducted as detailed in Appendix II, Section 2.

7.1.1 Screening Procedures Before Dosing

The following will be recorded in the CRF for subjects who have provided written consent (also assent if applicable):

- Demography (ethnicity, genotype and family history of haemophilia).
- Date of diagnosis and basal FVIII:C at diagnosis.
- Previous treatment regimen (prophylactic or on-demand).
- Bleeding history during the past year, including bleed frequency, severity, and treatment of bleeds -
- History of other FVIII containing products and/or blood products used within the past year.
- Dates of vaccination against hepatitis A and hepatitis B (if applicable).
- Medical and Physical examination including height and weight. The following body systems will be examined: Head, Ears, Eyes, Nose, and Throat (HEENT), chest, cardiovascular, respiratory, abdomen, musculoskeletal, genito-urinal, skin and general appearance.
- Current FVIII product (dose, start date)
- The date of the most recent dose of factor VIII, and actual dose.
- Blood samples will be taken for the following assessments:
    - HIV (central lab) (see Section 7.9.5)
    - CD4 count (central lab) (see Section 7.9.4)
    - Genotyping (if not available), (central lab) also see Section 7.9.6.
    - Pre-bolus FVIII:C assay (central lab) (see Section 7.9.1).
    - FVIII inhibitor screen and Nijmegen-Bethesda assay[#] (central lab)(see Section 7.9.2).

All FVIII inhibitor samples will be taken after a 3 day washout period.

7.1.2 Current FVIII Recovery Assessment

When all the above screening assessments have been completed eligible subjects who have not taken any FVIII replacement therapy for at least 3 days (*ie* a wash out period) and are not actively bleeding will undergo a recovery assessment using the subject's current FVIII concentrate. If an adequate wash out period has not been completed or if the subject is actively bleeding, the recovery assessment will be re-scheduled to occur within the 4 week Screening period.

Subjects who have completed a 3 day washout period and are not actively bleeding will be dosed with 30 IU/kg of their current FVIII. The dose will be measured to the nearest 0.1 mL.

All details of the dose calculation and dose administered, as described in Section 6.2, will be recorded in the CRF. The dose administered will be based on the subject's weight at this visit. After dosing the following post-infusion FVIII:C samples will be collected:

- 15 minutes post-infusion (±5 minutes [mins])
- 30 minutes post-infusion (±5 mins)
- 1 hour post-infusion (±10 mins).

Preferably, the arm into which FVIII/Optivate® is administered and the arm from which blood samples are taken should be different. However, if necessary, blood samples may be drawn from the same site as the infusion, including venous access devices *eg* portacath. In such cases the line/device should be flushed with saline (equivalent to 2 volumes of the dead space) and a volume of blood equivalent to 2 volumes of the dead space of the infusion line should be withdrawn before obtaining the blood samples. If the sample is drawn from the same site as the infusion, this must be documented in the CRF in case of spurious results. For full details on sample collection, labelling, processing and storage for all laboratory tests, please see the separate Laboratory Manual.

Actual times of sample collection will be recorded in the CRF.

Appendix III displays the maximum volume of blood allowed to be withdrawn in children according to their bodyweight. It is the Investigator's responsibility to ensure these limits are not exceeded.

All AEs will be recorded in the CRF (including any infusion site reactions and clinically significant changes in vital signs).

7.1.3 After Recovery Assessment

After the recovery assessment subjects will be:

- ✓ Issued with a study ID card or equivalent.
- ✓ Trained on how to use the study diary by the site staff before they are issued, the training will be noted in the hospital notes. Only subjects who are able to use the study diary correctly will be enrolled and allowed to continue in the study.
- ✓ Issued with a study diary manual
- ✓ Instructed to record current FVIII usage, bleed data, any AEs and if they take any medication other than current FVIIIinto the study diary throughout the study.

During screening and Baseline Visit (V1) subjects will continue to use their current FVIII therapy as previously and record bleeds, AEs and concurrent therapy in the study diary. The data on the study diary will be viewed by the site staff regularly (see study diary manual for further details).

Subjects will be reminded that they will need to bring their study diary with them at the next visit and to complete a 3 day washout period with their current FVIII concentrate prior to the next visit.

7.2 Baseline Visit (V1)

The visit will take place within 4 weeks of the Screening Visit.

All Screening Visit assessments should be repeated if the interval between the Screening Visit and the Baseline Visit is longer than 4 weeks. However, as long as the interval between the Screening Visit and the Baseline Visit is no longer than 8 weeks and in the case of children the maximum blood withdrawal volumes are not exceeded (Appendix III), these assessments may be combined with the Baseline Visit. In this case, initially previous screening laboratory results can be used to reassess subject's eligibility. In addition, all the required screening samples will be re-taken and sent to the central laboratory for processing. Then if the central results show that the subject is not eligible, they will be withdrawn from the study. The sites will also need to ensure the blood withdrawal volumes are not exceeded in such cases (Appendix III).

Subjects will receive their first dose of Optivate® at this visit.

7.2.1 Before Dosing of Optivate®

The following inclusion/exclusion criteria will be checked (laboratory results from the Screening Visit will be required for some criteria):

- Negative for inhibitors (a positive result is defined as a Nijmegen-Bethesda value of ≥ 0.6 BU/mL).
- A CD4 count > 200 /μL.
- Be HIV negative or a viral load of < 200 particles/μL.
- No other coagulopathy other than haemophilia A.
- No clinically significant symptomatic renal disease and/or (historical, within the last 12 months, serum creatinine > 200μmol/L).
- No clinically significant symptomatic liver disease and/or (historical within the last 12 months, serum ALT levels greater than three times the upper limit of the normal range).

The following procedures will also be conducted at this visit:

- Review any remaining study diary data; any queries on incomplete entries will be followed up with the subject and if required the subject will be re-trained on how to use the study diary.
- Review any changes in medical history or medication since the Screening Visit (any changes will be recorded as AEs).
- The date of the most recent dose of FVIII, actual dose (in IU/kg) will be recorded and the name of the factor VIII product.
- Body weight (kg).
- Blood samples for:
  - FVIII:C (pre-bolus) (see Section 7.9.1)
  - FVIII inhibitor tests (screen and Nijmegen-Bethesda assay)[#], see Section 7.9.2
  - Viral serology (see Section 7.9.5).
  - Archive sample. Serum sample for eventual storage at the Central Laboratory Archive at -70°C for 15 years (see Section 7.9.7).

all FVIII inhibitor samples will be taken after a 3 day washout period.

7.2.2 Dosing of Optivate® and Recovery Assessment

When all baseline pre-dose procedures have been performed, 30 IU/kg of Optivate® will be infused at a rate not exceeding 3 mL/minute. The dose selected will be infused to the nearest 0.1 mL.

All details of the dose calculation and dose administered, as described in Section 6.2, will be recorded in the CRF. The dose administered will be based on the subject's weight at this visit.

Optivate® FVIII:C recovery (at the same timepoints) and procedures as detailed in Section 7.1.2 will be conducted.

7.2.3 After Recovery Assessment

After the recovery assessment subjects will be given sufficient supply of Optivate® until the next visit. All subjects will start prophylactic treatment at a dose of 20-40 IU/kg three times a week, this dose will be monitored closely by the Investigator and if needed adjusted accordingly (also see Section 6.2.2.1). During this period the subjects will also administer doses to treat bleeds and for preventative use prior to increased physical activity (see dosing Section 6.2.2.2 and 6.2.2.3). The site staff will record the agreed doses of Optivate® to be administered on the subject's ID card. Subjects will continue to use the study diary as instructed, which will now include all Optivate® usage. The data on the study diary will be viewed by the site staff on a regular basis (see study diary manual for more details). Clinician's will need to review the bleed severity assigned for all break-through bleeds and provide a clinical judgement on the treatment outcome (also see Section 7.6 and 7.8).

Subjects will be reminded to complete a 3 day washout period, count the number of unused vials they have at home so they can update the site staff, and to bring in cartons from used vials and the study diary with them when they next attend the hospital.

Subjects will be instructed to contact the study centre if they are worried about the treatment or have excessive bleeding and in the case of an emergency bleed. If the Investigator suspects inhibitor development, the subject will be required to attend the main clinic more frequently and additional sampling will be conducted to assess the subject's progress.

7.3 Visit 2 and Visit 3

Visit 2 will take place 4 weeks after the Baseline Visit (Visit 1). It is estimated the subjects would have reached between 10 and 15 EDs by this visit.

Visit 3 will take place 3 months after the Visit 2 (4 months after V1). It is estimated the subjects would have reached between 50 and 75 EDs by this visit.

If the minimum EDs have not been reached for the above visits, then the visits will be re-scheduled.

Optivate® recovery assessments will be conducted at these visits as previously described (section 7.1.2 and 7.2.2).

7.3.1 Before Dosing of Optivate®

The following procedures will also be conducted at these visits:

- Review of any remaining study diary data.
- Review of any changes since the last visit *eg* AEs, concomitant medication.
- Body weight (kg).
- The date of the most recent dose of Optivate® will be recorded. If subjects have taken Optivate® within the washout period or are actively bleeding, then the recovery assessment will be rescheduled.
- Blood samples for:
  - FVIII:C (pre-bolus), see Section 7.9.1
  - FVIII inhibitor tests (screen and Nijmegen-Bethesda assay)#, See Section 7.9.2.

all FVIII inhibitor samples will be taken after a 3 day washout period.

7.3.2 Dosing of Optivate® and After Recovery Assessment

When all the pre-dose procedures have been performed, 30 IU/kg of Optivate® will be infused at a rate not exceeding 3 mL/minute and an Optivate® recovery assessment (at the same timepoints) and subsequent post recovery procedures as detailed in Section 7.1.2 and 7.2.3 will be conducted.

7.4 End-of-Study Visit (V4)

This visit will take place once the subject has completed at least 100 EDs, which is estimated to occur between 9 to 12 months (39 to 52 weeks) after the Baseline Visit (V1).

The final Optivate® recovery will be conducted at this visit.

Subjects who withdraw prematurely from the study will also undergo the same End-of Study safety assessments as those subjects that have completed the study (see Section 9).

7.4.1 Before Dosing of Optivate®

The following procedures will be conducted:

- Subjects will return all remaining unused IMP and cartons of the used vials for an accountability check.
- Review any remaining study diary data.

- Review of any changes since the last visit *eg* AEs, concomitant medication.
- Brief physical and medical examination, including height and weight (see Section 8.2.4).
- The date of the most recent dose of Optivate® will be recorded. If subjects have taken Optivate® within the washout period or are actively bleeding, then the recovery assessment will be rescheduled.
- Blood samples collected for :
    - FVIII:C (see Section 7.9.1)
    - FVIII inhibitor screen and Nijmegen-Bethesda assay (see Section 7.9.2)
    - Viral serology (see Section 7.9.5).
    - Archive sample. Serum sample for eventual storage at -70°C for 15 years (see Section 7.9.7).

7.4.2 Dosing of Optivate® and After Recovery Assessment

When all pre-dose procedures have been performed, 30 IU/kg of Optivate® will be infused at a rate not exceeding 3 mL/minute and an Optivate® recovery assessment (at the same timepoints) and procedures detailed in Section 7.1.2 will be conducted.

7.4.3 After Recovery Assessment

After the recovery assessment the Investigator will complete the end of study page on the CRF and the subject will be discharged from the study, when they can continue on Optivate® therapy using commercially available vials or return to using their previous FVIII therapy.

7.5 Safety Follow-Up (FU) (telephone contact) – 28 days after last Optivate® infusion

Twenty-eight days after the last infusion of Optivate® the site staff will contact the subject by telephone to follow-up on any AEs. Any SAEs occurring within 28 days after the last dose of Optivate® will be reported according to procedures outlined in Appendix I.

7.6 Treatment of Bleeds

If a subject experiences a spontaneous bleed or bleeding due to injury or post trauma these will be recorded in the study diary. Treatment should be administered as per Section 6.2.2.2 and if subjects are concerned about any excessive bleeding or have an emergency bleed they should contact the Investigational site (study centre). If required, the subject will be asked to attend the hospital for review.

During home therapy subjects will enter bleed data into the study diary, and the data will be reviewed by the site staff on a regular basis (see study diary manual for more details). For each bleed the subject will assign severity of a bleed (major, minor or emergency), which will be reviewed by the clinician. For the purposes of this study a major bleed is defined as a bleed that unacceptably restricts the patient's day-to-day life and an emergency bleed requires immediate medical attention. If the clinician disagrees with assigned severity this will be discussed with the subject and an agreed severity for the bleed will be recorded in the study diary. The clinician should make every effort to come to an agreed assessment of severity of the bleed. However, if severity cannot be agreed, then the clinician's medical review of severity will be recorded onto the study database and a comment added on the study database and hospital notes stating that the subject did not agree with the severity assigned by the medical staff. Treatment outcome with Optivate® therapy will be assessed by the subject and clinician separately (see Sections 7.8 and 8.1.2.3).

7.7 Unscheduled Visits

These visits are additional to the scheduled visits detailed in the trial flow chart (Appendix VI).

7.7.1 Excessive Bleeding Visit or After an Emergency Bleed

During home therapy subjects will assign bleed severity as major, minor and emergency, where a major bleed is defined as a bleed that unacceptably restricts the patient's day-to-day life and an emergency bleed is one which requires immediate medical attention. Also see Section 7.6.

If any subject is concerned about their treatment or has excessive bleeding or an emergency bleed they must contact the Investigational site.

If the subject has recently had surgery and the excessive bleeding is a result of the surgery this will be recorded in the CRF as an adverse event.

If required the subject will attend the Investigational site, and the following procedures will be conducted:

- Review of changes since the last visit (*eg* AEs).
- Blood samples will be collected for:
    - FVIII:C assay. Samples will be assayed at the central and local laboratory, to help manage the subject locally until the central results are made available. Also see Section 7.9.1 and for further details the Laboratory Manual.

  - FVIII inhibitor screen and Nijmegen-Bethesda assay (see Section 7.9.2).
- The Investigator must assess the bleed severity and efficacy of Optivate® in treating the bleed (see Sections 7.6, 7.8 and 8.1.2.3).

7.7.2 Other Visits

Subjects may also attend the Investigational site as required for:

- Collection of repeat blood samples, if required.
- Additional FVIII inhibitor tests and recovery assessment, if an inhibitor is suspected/confirmed.
- Additional Optivate® supplies.
- Clinical observations (routine visits or as part of the study).
- Advice on study treatment.

7.8 Study Diaries

After the screening assessments have been conducted all subjects will be given a study diary to use during the study. The study diary is to enable comprehensive record of health information consistently for all subjects. In addition, subjects will be provided with a study diary manual explaining how to record the data and how this data needs to be returned to the site for regular review (see the study diary manual for more details).

The study diaries are to be completed when the subject has an adverse event or takes Optivate® or other medication (except herbal and homeopathic remedies) at home or at a local clinic (*ie* not the Investigational site) and with bleed details.

The diaries will record the following information:

- Optivate usage (home or at a local clinic).
- Details of any other AEs which occurred during home therapy. AEs that occur at site will be recorded on the CRF by the site staff; these will not be entered into the study diary to avoid duplication.
- Details of concurrent medication (excluding vitamins and herbal and homeopathic remedies) including name (preferably the generic name), dose, start date and stop date.
- Details of bleeds:
  - Duration (bleed start and stop time)
  - Location (joint, muscle or open/other).
  - Severity (major, minor or emergency). A major bleed is defined as a bleed that unacceptably restricts the patient's day-to-day life and an emergency bleed requires

urgent medical attention. In the case of emergency bleeds the study centre will be contacted. Clinicians will also review this data regularly and amend if necessary after discussing it with the subject (see Section 7.6).

- New bleed or ongoing bleed
- Cause (spontaneous bleeding, injury or other).
- Subjects will assess Optivate® therapy for each bleed as:
    - Very Helpful
    - Helpful
    - Helped a little
    - Did not help
- The Investigator will also be assess Optivate® therapy for each bleed as:
    - Excellent
    - Good
    - Moderate
    - Poor

The study diaries will also record the following details of each dose of Optivate® administered at home or at the local clinic:

- Date and time of dose.
- Batch number.
- Whether the dose was administered as a preventative dose, a routine prophylactic dose or to treat a bleed.

Between visits data from the study diary will be reviewed by site staff on a regular basis (see study diary manual for more details) and then again at each visit. The Investigator must review severity and assess Optivate® therapy in treating the bleed, as stated above. **It is the Investigator's responsibility to ensure that the study diaries are completed correctly and that all clinically relevant information is recorded.** Any queries on the study diary data will be addressed with the subject as soon as possible, by telephone or by calling the subject into the hospital. If required subjects will be re-trained on how to use the study diary. This training and related discussions will be documented in the hospital notes.

Only subjects who are able to use the study diary correctly will be enrolled and allowed to continue in the study.

7.9 Blood Sample Collection, Handling and Shipping

For more detailed information on the handling of samples for the study, refer to the Laboratory Manual.

7.9.1 FVIII:C Recovery Sample Collection

All FVIII:C recovery blood samples will be collected at the Investigational site. Samples will be processed and frozen immediately. These will be shipped to a Central Laboratory under frozen conditions and then sent to Haematology Department, Addenbrooke's Hospital, Cambridge, UK for processing. All patient samples will undergo testing to evaluate in-vivo FVIII:C recovery using a one-stage clotting assay. In addition, a chromogenic assay will also be used only for the first Optivate® recovery assessment at visit 1.

Further details on the handling, storage and shipment of samples can be found in the Laboratory Manual.

7.9.2 FVIII Inhibitors

Both a FVIII inhibitor screen and a quantitative FVIII Nijmegen-Bethesda inhibitor test will be performed at Addenbrooke's Hospital, UK. All inhibitor samples will be collected after a 3 day washout period, when it is anticipated that the pre-substitution FVIII level has reached a nadir[12].

FVIII inhibitor screening test

For the FVIII inhibitor screens, an APTT is performed on a 50/50 mix of a subject's plasma and normal pooled plasma, and compared with the APTT for the subject's plasma and that of normal pooled plasma. A positive inhibitor screen is defined as one that does not correct the APTT by > 50% of the difference between the subject's value and the normal pooled plasma value. To rule out the presence of a time-dependent inhibitor, 50/50 mixes of the subject's plasma and normal plasma are compared following incubation together or separately for 2 hours at 37ºC. Time-dependent inhibition is defined as > 4 seconds' prolongation of the incubated mixture relative to the plasmas incubated separately.

FVIII Nijmegen-Bethesda inhibitor test

A Nijmegen-Bethesda assay will also be performed using the same sample as above. A result of ≥ 0.6 BU confirms that the subject has developed inhibitors to FVIII. If this occurs, the test will be repeated on a separate sample; if both tests are confirmed to be ≥ 0.6 BU this will be reported by

the Investigator as an SAE (see Appendix I). The Central Laboratory will notify both the Contract Research Organisation (CRO) and Sponsor immediately if any sample has a value of ≥ 0.6 BU, even if the repeat analysis has not been conducted.

If there is a discrepancy between the FVIII inhibitor screen and Nijmegen-Bethesda assay result, analyses will be repeated on reserve samples and, if necessary, additional samples from the subject, until an unequivocal result, or a reason for the discrepancy, is obtained.

If necessary, repeat FVIII inhibitor quantitative assays will be performed on reserve samples from earlier timepoints, in an attempt to identify the point at which an immune response was initiated. The subject's progress will be monitored closely and if any additional FVIII inhibitor samples are required, these should be taken in triplicate to allow repeat testing and assessment of possible 'transient' inhibitors.

If required, additional methodologies may be used to detect and quantitate inhibitors to FVIII. Any such methodologies will be described in detail in the clinical study report.

Further details on the handling, storage and shipment of samples can be found in the Laboratory Manual.

7.9.3 Reserve Samples

At each recovery timepoint (see Appendix VI) and where blood samples are collected for FVIII:C and FVIII inhibitor assay, a reserve aliquot of plasma will be stored, for reanalysis if needed, *eg* if an original sample is spoiled or if results are discrepant. See Appendix VI and Laboratory Manual.

Reserve samples will be stored at the study site at -70°C for the duration of the study and sent to a central location when requested by the Sponsor. Alternatively, where -70°C storage facilities do not exist, reserve samples may be stored at the study site at -20°C and sent to a central location within one month of collection. Reserve samples may be kept at -70°C until the last licence for Optivate® is granted in the EU and will be used, if required, for repeat or additional assays at the request of a regulatory agency.

7.9.4 CD4 Count

A blood sample to measure the subject's CD4 level and check eligibility will be collected at screening visit only.

7.9.5 Virology Samples

HIV sample will be collected at Screening to check eligibility. Full viral serology will be conducted at Baseline and End-of-Study. Samples will be tested for the following panel of markers:

- Anti-HIV1
- Hepatitis B Surface Antigen (HBsAg)
- Anti- Hepatitis C Virus (HCV)
- Anti- Hepatitis A Virus (HAV) (Immunoglobulin M [IgM])
- Anti- Hepatitis A Virus HAV (Immunoglobulin M [IgG])

If there is a change in any of the above serological markers during the study for any subject (which includes the most recent pre-study result), this must be reported to the Sponsor within 24 hours of receipt of results at the study site, regardless of whether it meets the seriousness criteria described in Appendix I.

For more details on the handling of samples for viral serology, see the Laboratory Manual.

7.9.6 Genotype

Genotype analysis performed prior to the study will also be acceptable. If genotype has not already been performed then this will be conducted at screening. The analysis will be performed at the Centre for Haemostasis and Thrombosis, St Thomas' Hospital, London, UK. A single whole blood sample will be collected. The specific mutation(s), date of analysis and name of laboratory at which the analysis was performed, will be recorded in the CRF.

7.9.7 Archive Samples

An archive serum sample will be collected pre-dose at the Baseline Visit (V1) and at the End-of-Study Visit (V4). Archive serum samples will be sent to the Central Laboratory for storage at -70^{o}C and later batch shipment to a central laboratory archive for long-term storage at -70^{o}C for 15 years. The archive sample serves as a safety measure for subjects receiving human plasma-derived product, for investigation of risk factors which may potentially be identified in the future and is required by current CHMP guidelines for coagulation factors[12].

7.9.8 Volume of Blood Collected for Children

Appendix III displays the maximum volume of blood allowed to be withdrawn from children according to their bodyweight. During the study it will be the Investigator's responsibility to

ensure these limits are not exceeded and if necessary ensure visits are re-scheduled accordingly and the study monitor notified. See Laboratory Manual for the volume of blood taken at each visit.

No more than 2 tablespoons of blood will be collected at one visit. A tablespoon of blood is defined as 15mL. In the case of young children this can be reduced further to avoid exceeding the maximum withdrawal volumes (see Appendix III and Laboratory Manual).

7.10 Recording and Reporting Laboratory Results

Central Laboratory data will be faxed to the Investigator. All reports must be reviewed by the Investigator as soon as possible after receipt, and signed and dated by the Investigator. Any values outside the normal range should be assessed for clinical significance. Any considered to be clinically significant by the Investigator must be commented upon. For further information on the tests to be performed see Sections 7.9.

FVIII:C and FVIII inhibitor test results will be sent by the Central Laboratory to the Sponsor for ongoing recovery data collection and analysis. This will be used to review recovery assessment and monitor the development of inhibitors throughout the study.

The Sponsor will be notified immediately if there are any positive inhibitor results or changes in viral serology during the study.

7.11 Data Recording and Reporting

It is the Investigator's responsibility to ensure that all data to be collected at each visit is recorded in the subject's hospital notes as 'source data'.

7.12 Restrictions

There are no dietary or exercise restrictions in this study. The use of other products containing FVIII and antifibrinolytics agents (except during surgery) is prohibited during the trial. However, if the subject requires surgery and an antifibrinolytic agent needs to be administered *eg* dental surgery, this is permitted. In such cases the exposure days during surgery will be excluded from the Optivate® ED calculations. There are no further concurrent therapy restrictions.

8 OUTCOME MEASURES

8.1 Efficacy Measures

All subjects who received at least one dose of Optivate® will be included into the efficacy analysis.

If subjects suffering with severe haemophilia A with a basal FVIII of < 2% are recruited into the study, as per the CHMP guidelines[12], in addition to the analysis for all subjects, separate analyses will also be conducted for subjects with a basal FVIII of < 1% and then for subjects with a basal FVIII of < 2%.

8.1.1 Primary Efficacy Variable

The primary efficacy variable is assessment of the immunogenicity of Optivate® by monitoring plasma inhibitor levels for at least 100 EDs for each subject.

Factor VIII inhibitor screens and Nijmegen-Bethesda assays

Pre-bolus blood samples for FVIII inhibitor screens and quantitative assays will be collected at the Screening Visit, Baseline Visit (V1), V2, V3 and the End-of-Study Visit (V4), and at any unscheduled Visit conducted because of excessive bleeding or following an emergency bleed.

In accordance with the CHMP guidelines, results from a recovery assessment will also be required to confirm an inhibitor[12], in addition to the inhibitor test (see Section 7.7.2).

8.1.2 Secondary Efficacy Variables

8.1.2.1 Current FVIII Recovery vs. 1st dose of Optivate® Recovery (V1)

All recoveries will be calculated from incremental FVIII values (i.e. actual values minus pre-infusion values) and the vial content as provided by BPL will be used to calculate the recovery dose. FVIII values of less than 0.01 IU/ml will be regarded as zero. Incremental recovery will be determined from the peak value reached within the first hour. Calculations will be based on the peak values obtained at actual post-infusion times, rather than those scheduled in the protocol.

$$\text{Recovery} = \frac{\text{FVIII increment (IU/dL)}}{\text{FVIII dose (IU/kg)}}$$

Results will be tested for the normality of distribution using the Shapiro-Wilk test and if normality is confirmed, an Analysis of Variance (ANOVA) will be performed for the above recovery comparison.

8.1.2.2 Optivate® Recovery Over Time

For V1 (1 ED), V2 (10-15 ED), V3 (50-75 ED) and V4 (100 ED) recovery will be calculated using the formula in 8.1.2.1. An overall Optivate® recovery value will be calculated across the whole study and for each batch on a per subject basis. An ANOVA will also be performed to compare recovery values at V1, V2, V3, and V4 and across batches.

8.1.2.3 Optivate® Therapy to Treat Break Through Bleeds

The following will be assessed:

1. The number of break-through bleeds including:
    a. severity (major, minor, emergency)
    b. duration
    c. location (joint, muscle, open/other)
    d. cause (spontaneous, injury, other).
2. Clinician's judgement of break-through bleed treatment outcome (Excellent, Good, Moderate, Poor).
3. Subject's judgement of break-through bleed treatment outcome (very helpful, helpful, helped a little, did not help).

8.1.2.4 Overall Consumption of Optivate®

1. Number of exposure days for each subject and per month/subject, per year/subject and overall.
2. Total dose in IU/kg of Optivate® and average dose per infusion for prophylactic use, to treat a bleed, any additional preventative use and overall use; all analysed on a per subject basis.
3. Total number of infusions for prophylactic use, to treat a bleed, any additional preventative use and overall use; all analysed on a per subject basis.
4. Mean dose in IU/kg of FVIII per subject/month and per subject/year prophylactically, to treat a bleed, any additional preventative use and overall use; all analysed on a per subject basis.
5. Mean number of infusions per subject/month and per subject/year for prophylactic use, to treat a bleed, any additional preventative use and overall use; all analysed on a per subject basis.

For calculation purposes, a month will be defined as 28 days and a year will be defined as 365 days. Where a subject has completed less than a year of Optivate® treatment, the data will be extrapolated to calculate the per consumption per year.

8.1.2.5 Genotype Analysis

Genotype data will be collected at screening (also see Section 7.9.6) and the data on mutation type for each subject will be listed.

8.2 Safety Variables

All subjects who received at least one dose of Optivate® will be included into the safety population The following will be used to assess the safety of Optivate®:

- AEs, product-related AEs, serious ADRs
- Viral serology
- Physical/Medical examination.
- Inhibitor development (this is a safety measurement and will be accessed as a primary efficacy endpoint, see Section 8.1.1).

8.2.1 Adverse Events

All the adverse events data (from CRF and study diary) will be pooled together and reported in terms of the type, duration, treatment and/or severity. For further information on the definition and reporting of adverse events, see Appendix I.

All adverse events (product related or unrelated) that appear or worsen during the course of the study will be captured on the database. If an AE occurs at the study site this will be recorded in the CRF. If an AE occurs during home therapy this will be recorded in the study diary to avoid duplicate entry. This data will be pooled in the final analysis. If a subject has a recurring condition, whether related to FVIII deficiency or not, then this should be recorded at the Screening Visit in the Medical History pages of the CRF.

Fluctuations or re-occurrences of the condition, that are considered normal for the subject and are recorded in the medical history, need not be reported as an adverse event. However, if the condition were to deteriorate during the study this would then be recorded as an adverse event.

If surgery is planned before entry into the study, the indication for surgery should be recorded in the medical history, and this will not be reported as an adverse event, unless the planned hospitalisation is prolonged. Dosing during surgery should be as per the Optivate® SmPC[1] and Section 6.2.3. The use of antifibrinolytic agents is prohibited during the trial, however if these are necessary during surgery then this will be allowed. In such cases the exposure days during surgery

will be excluded from the Optivate® EDs calculations. Both the CRA and the Sponsor will need to be notified if antifibrinolytic agents are used. If an AEs is considered to be related to surgery or is a complication of surgery this will be specified on the AE the form. If the AE meets the definitions of a Serious Adverse Event (see Appendix I) this will be reported as a SAE. A narrative will be written for each surgical procedure.

A spontaneous bleed will not be reported as an adverse event, unless it represents a consistent worsening of factor VIII deficiency symptoms or the subject is hospitalised. Any excessive bleeding as a result of the surgery will be recorded as an AE. Bleed details will be recorded in the study diary and checked by site personnel.

8.2.2 CD4 Count

CD4 counts will be assessed by the Central Laboratory. Blood samples for CD4 count assessments will only be collected at the Screening Visit to assess subject's eligibility.

8.2.3 Viral Serology

Viral serology variables will be assessed by the central safety laboratory (see Section 7.9.5 for list of markers tested in the study). A blood sample to test for HIV will be collected at screening, to assess the subject's eligibility. Serum samples for all viral serology testing will be collected pre-dose at the Baseline Visit (V1) and at the End-of-Study Visit (V4). Any changes in serology during the study period will be reported to the Sponsor immediately.

8.2.4 Physical/Medical Examination

A physical/medical examination including weight and height will be performed at the Screening Visit and the End-of-Study Visit (V4). The following body systems will be examined: HEENT, chest, cardiovascular, respiratory, abdomen, musculoskeletal, genito-urinal, skin and general appearance.

Any changes from the Screening Visit to the End-of-Study Visit (V4) will be recorded in the CRF. Any adverse change in the physical examination will be reported as an adverse event.

Body weight will also be recorded at all visits to allow for calculation of an exact dose in IU/kg.

9 SUBJECT WITHDRAWAL

Subjects may stop study treatment for any of the following reasons:

- Withdrawal of consent.

- Significant protocol deviation.
- Lost to follow-up.
- Incidental illness.
- Occurrence of adverse events (AEs) not compatible with the continuation of the subject's participation in the study, in the Investigator's opinion (*eg* anaphylactic or other severe/serious reaction to infusion, development of inhibitor).
- Investigator's request.
- Requirement for therapeutic intervention prohibited by the protocol *eg* FVIII containing product or antifibrinolytics agents (expect during surgery).
- Premature termination of the trial by BPL on account of an unacceptable risk-benefit ratio. If this occurs, BPL or BPL's representatives will notify the regulatory authorities, ethics committees and Investigators of the reason for premature study termination, within 15 days from the study being halted.
- Subject/guardian is unco-operative and non-compliant with respect to provisions of the protocol.
- Trial stopped by BPL as 10 evaluable subjects have 100 EDs with Optivate®. **NB:**this may mean that the last two subjects enrolled into the study may receive a shorter treatment period.

The clinical Investigator may also remove a subject if, in his/her opinion, it is in the best interests of the subject.

Subjects are free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The reason(s) for withdrawal will be documented where possible, particularly where withdrawal is a consequence of an adverse event. The subject's primary care physician (where applicable) will be informed of the reason for withdrawal.

Data collected up until a subject's withdrawal from the study, including data for screen failures, will be retained on the clinical database and used in the analysis and clinical study report.

Subjects withdrawing from the study will be requested to complete the same final assessments as subjects completing the study according to the protocol, particularly safety assessments (see Section 7.4). If there is a medical reason for withdrawal, the subject will remain under the supervision of the Investigator until in satisfactory health or the subject's condition has stabilised.

Reasonable efforts will be made to contact subjects who are lost to follow-up. These efforts must be documented in the subject's medical records.

10. DATA ANALYSIS

10.1 Source Data

The collection and analysis of high quality data is dependent on accurate documentation in the subject's hospital notes, to allow accurate verification of CRF data. See Appendix II (Administrative Requirements) for more detail on the recording of data in subject's notes and maintenance of other study documents.

To avoid duplicate entry of AEs which occur at the study site these will be recorded in the CRF. AEs which occur during home therapy these will be recorded in the study diary.

10.2 Data Management and Coding

The CRO selected Data Management Group will be responsible for activities associated with the data management for the final analysis. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Missing or inconsistent data will be queried in writing to the Investigator for clarification. Subsequent modifications to the database will be documented.

10.3 Statistical and Analytical plans

All tables, figures and listings will be produced using the most recent version SAS (Statistical Analysis System).

Unless otherwise stated, categorical data will be presented using counts and percentages, whilst continuous variables will be presented using the mean, 95% confidence interval for the mean, standard deviation (SD), median, minimum, maximum, number of subjects (n) and number of missing subjects or datapoints. Minima and maxima will be quoted to the number of decimal places as recorded in the CRF; means, and medians will be quoted to one further decimal place. SDs will be quoted to one further decimal place than the mean value. Percentages will be rounded to one decimal place.

The efficacy analysis will be performed for the per protocol population, and the safety population will be used to report all safety data, in accordance with the statistical analysis plan (SAP). Demographic data will be reported for the safety population.

All data will be listed. More information is in the SAP for the study.

10.4 Analysis Populations

The following analysis populations will be defined for this study.

If subjects suffering from severe haemophilia A with basal FVIII values of < 2% rather than < 1% are recruited into the study, in addition to the analysis for all subjects, two separate analyses will be conducted: One for subjects with a basal FVIII < 1%, the other for subjects with a basal FVIII < 2%.

Safety Population

The safety ITT population will be defined as all subjects who received at least part of one dose of Optivate®. Safety data will be analysed up to the point of withdrawal for subjects who withdraw, if the number of points is adequate to allow a scientific analysis.

Per Protocol Population

The per protocol population will be defined as all subjects who have completed a minimum of 100 EDs with Optivate®.

NOTE: If antifibrinolytic agents have been administered during surgery, the surgery exposure days will not be included in the Optivate® ED calculations.

The efficacy analysis will include all the subjects in the per protocol population. The secondary analysis will include all subjects in the ITT population.

10.5 Demographics and Other Baseline Characteristics

Demographic data, including age, sex, height, weight and ethnic origin will be summarised. These will be displayed in the following age groups:

- Less than 12 years
- Greater than and equal to 12 years
- All subjects

Baseline characteristics, including family history of haemophilia, historical disease data and diagnostic information will be summarised as appropriate.

10.6 Efficacy

All primary and secondary endpoints will be tabulated.

10.6.1 Primary Endpoint

The primary efficacy endpoint is to assess immunogenicity of Optivate® by monitoring plasma inhibitor level for at least 100 EDs for each subject.

FVIII inhibitor evaluation

FVIII inhibitor screen data will be listed. FVIII quantitative inhibitor results will be listed. Shift tables will present the number of subjects with positive (≥ 0.6 BU) and negative (< 0.6 BU) results and those for whom the results change during the study. The number of exposure days until development of inhibitors will be summarised.

10.6.2 Secondary Endpoints

The secondary efficacy endpoints are the parameters described in Section 8.1.2 and safety variables in Section 8.2.

Recoveries

Results will be tested for the normality of distribution using the Shapiro-Wilk test and if normality is confirmed, an ANOVA will be performed for the recovery comparison (See Section 8.1.2.1 and 8.1.2.2).

Descriptive statistics will be presented on the number of recoveries at each timepoint and for each subject. These will be presented for each visit and for each subject and then for each batch of FVIII/ Optivate® used (see Section 8.1.2.1 and 8.1.2.2). Overall descriptive statistics will also be present for all subjects and all batches.

Bleeds

Bleed data will be summarised using summary statistics on two different bases: with each bleed as the experimental unit, and also with each subject as the experimental unit. Severity, duration of bleed, location and cause of bleed will be summarised separately, as well as being summarised in total. The treatment of new bleeds and ongoing bleeds will be listed. Also see Section 8.1.2.3.

Clinician's and subject's judgement of break-through bleed of treatment outcome

The data for clinician's and subject's assessment of bleeds will tabulated on separate tables, including the count for the number of bleeds not assessed. The tables will display the number and percentage of bleeds assessed for each category (*eg* very helpful, helpful etc.). This will be presented: Using all bleeds as the denominator and also the number of bleeds assessed as the denominator, displaying the number of bleeds not assessed.

Optivate® consumption

Dosing data will be summarised by treatment type *ie* prophylactic, preventative, to treat a bleed and overall. Total consumption data will be summarised using summary statistics on a per infusion and a per subject basis. Overall consumption data will be listed for each subject and summary statistics will also be displayed per month and year on a per subject basis (also see Section 8.1.2.4). Where a subject has completed less than a year of Optivate® treatment, the data will be extrapolated to calculate the per year consumption.

Exposure days

An exposure day is defined as a day in which the subject has received at least one dose of Optivate® (irrespective of treatment). The number of EDs will be listed for each subject. Descriptive statistics will be presented on a per month, per year and overall basis (also see Section 8.1.2.4).

NOTE: If antifibrinolytic agents have been administered during surgery, the surgery exposure days will not be included in the Optivate® ED calculations. Where a subject has completed less than a year of Optivate® treatment, the ED data will be extrapolated to calculate per year value.

Surgical Procedures

Descriptive narratives will be written for each surgical procedure and appended to the Clinical Study Report.

10.7 Safety Variables

The general strategy of the safety evaluation will be to examine the summaries for any trends. No formal hypothesis testing will be carried out.

10.7.1 Adverse Events

Adverse events (AEs) will be coded by the MedDRA (Medical Dictionary for Regulatory Authorities) system organ class and preferred term. Only treatment emergent AEs (*ie* beginning after dosing with Optivate®) will be included in the summary tables. All AEs (CRF and study diary) will be included in the data listings.

A bleed will not be reported as an adverse event, unless it represents a consistent worsening of FVIII deficiency symptoms or the subject is hospitalised. Bleed details will be recorded in the study diary by the subject. However, any excessive bleeding as a result of the surgery will be recorded as an adverse event.

Any complications of surgery that meet the definitions of a Serious Adverse Event (see Appendix I) will be reported as a Serious Adverse Events.

Adverse Drug Reactions (ADRs) will be defined as AEs which are recorded as having a possible, probable or very likely/certain causality related to Optivate®. If the Investigator cannot assign severity or causality as described in Appendix I, BPL will class the event as related. AEs leading to withdrawal will be defined as events where the Optivate® was discontinued as a result of the AE.

The denominator used for the calculation of percentages will be the number of subjects in the safety population. For all AE summaries described below, counting will be performed by subjects and event. For counts by subject, subjects experiencing the same event more than once will have that event counted only once within each system organ class and once within each preferred term.

The following summaries of treatment-emergent AEs will be provided:

Summary of AEs

All the AE data (from CRF and study diary) will be pooled together and reported in terms of the type, duration, treatment and/or severity.

The number and percentage of subjects reporting AEs, serious AEs (SAEs), ADRs, AEs leading to withdrawal and AEs leading to death. The number of AEs, SAEs, ADRs, AEs leading to withdrawal and SAEs leading to death.

Summary of AEs by Severity of Event

The number and percentage of subjects reporting AEs and ADRs, will be summarised by system organ class and by preferred term. The severity of event will be recorded once per subject for each preferred term as the maximum severity experienced by each subject (*ie* where the order of most severe to least severe is given by: severe, moderate then mild).

Summary of AEs by Causality

The number and percentage of subjects reporting AEs will be summarised by system organ class and by preferred term. The causality will be recorded once per subject for each term giving the most likely relationship to Optivate® (*ie* in the order: very likely/certain, probable, possible, unlikely, and unrelated).

10.7.2 Viral serology variables

Shift tables for virology will present the number of subjects with positive and negative serology results and those for whom the results change during the study.

10.7.3 Physical/Medical Examination

Physical/Medical examination details will be listed. Any adverse change will be reported as an adverse event, as described in Section 10.7.1.

10.8 Determination of Sample Size

No formal sample size calculation was performed, as no formal hypothesis testing is planned. The sample size of 10 evaluable subjects was agreed with the German regulatory authority as part of the licencing agreement for Optivate®. Therefore for this study 12 subjects will be enrolled to ensure data for 10 evaluable subjects.

11. INVESTIGATOR'S STATEMENT

Multicentre, Non-controlled, Prospective, Post-Marketing Safety Study Following Long-Term Prophylactic Optivate® Treatment in Subjects with Severe Haemophilia A.

STUDY CODE: 8VWF07

FINAL PROTOCOL

Version 4, 30 November 2015

I have been adequately informed about the development of the IMP to date and agree that this study protocol contains all the information required to conduct the study.

I will provide copies of the study protocol and all product information relating to prior product experience furnished to me by the Sponsor/CRO to all staff responsible to me who participate in this study. I will discuss this material with them to ensure that they are fully informed regarding the product and the conduct of the study.

The information contained in this document is CONFIDENTIAL and, except to the extent necessary to obtain informed consent, may not be disclosed, unless such disclosure is required by government regulation or local customs or law. Persons to whom the information is disclosed must be informed that the information is CONFIDENTIAL and cannot be disclosed by them.

By my signature below I agree to conduct this clinical trial in accordance with the protocol, Good Clinical Practice (GCP), government regulations, and local customs or laws, including those applying to institutional/ethics review and informed consent.

I agree to ensure the confidentiality of the subjects enrolled under my care; however, I agree to make their medical records available to authorised representatives of the CRO; authorised representatives of Bio Products Laboratory Ltd., the sponsor of this clinical trial; and relevant regulatory authorities.

I have read the Summary of Product Characteristics for Optivate® and protocol, and I am aware of my responsibilities as a Principal Investigator.

Signature: _____ Date: _____
Principal Investigator

Name: _____
(Printed)

12. REFERENCES

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APPENDICES

APPENDIX I - ADVERSE EVENT DEFINITIONS AND REPORTING PROCEDURES

ABBREVIATIONS

ADR	- Adverse Drug Reaction
AE	- Adverse Event
BPL	- Bio Products Laboratory Limited
CRF	- Case Record Form
e-CRF	- Electronic Case Record Form
ECG	- Electrocardiogram
ICF	- Informed Consent Form
IEC	- Independent Ethics Committee
IRB	- Institutional Review Board
IMP	- Investigational Medicinal Product
MHRA	- Medicines and Healthcare Products Regulatory Agency
SAE	- Serious Adverse Event
SmPC	- Summary of Product Characteristics
SUSAR	- Suspected Unexpected Serious Adverse Reaction

1. DEFINITIONS OF ADVERSE EVENTS

1.1 Adverse Event (AE)

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign including an abnormal laboratory (or vital sign, ECG, etc.) finding, symptom or disease temporally associated with the use of an investigational medicinal product (IMP). All adverse events, whether or not considered by the Investigator to be related to the IMP (test product, comparator or placebo), must be described and recorded on the appropriate Adverse Event forms in the CRF. Where possible, a diagnosis should be made. Anticipated fluctuations of pre-existing conditions, including the disease under study that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

Clinical Laboratory and Other Adverse Events

If a laboratory result is considered by the investigator to be clinically significant or have a clinically significant pathological change from baseline it should be recorded as an AE.

Other abnormal results (e.g. x-rays, scans, physical examination findings) that worsen from baseline and/or are considered clinically significant should also be recorded as AEs.

The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

AEs should be reported and documented in accordance with the procedures outlined below. All AEs occurring during the study must be documented on the relevant CRF/e-CRF pages. The following data should be documented for each AE:

- Description of the symptom event
- Classification of 'serious' or 'not serious'
- Severity
- Date of first occurrence and date of resolution (if applicable)
- Action taken
- Causal relationship
- Outcome of event (unknown, recovered, not yet recovered, recovered with sequelae, death [with date and cause reported])

Pregnancy

Subjects will be instructed that known or suspected pregnancy occurring during the study should be reported to the investigator. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. If a subject is found to be pregnant after inclusion in the study, the subject must be withdrawn from the study. Any pregnancy will be followed to term and the status of mother and child will be reported to the Sponsor after delivery.

Full details of any pregnancy will be recorded on the AE page of the CRF/eCRF, and a Pregnancy Report Form will be completed. A copy of the Pregnancy Report Form must be completed and faxed to the appropriate contact (as detailed in the Safety Management Plan) within 24 hours.

1.2 Adverse Drug Reaction (ADR)

All noxious and unintended responses to a medicinal product related to any dose administered. The phrase 'response to a medicinal product' means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

1.3 Serious Adverse Event (SAE) or Drug Reaction

A **Serious Adverse Event or reaction** is any untoward medical occurrence that at any dose:

- **results in death,**
- **is life-threatening (patient at risk of death at time of event; not hypothetically life-threatening),**
- **requires inpatient hospitalisation or prolongation of existing hospitalisation,**
- **results in persistent or significant disability or incapacity,**
- **is a congenital anomaly or birth defect,**
- **is an important medical event (see below for definition).**

The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Medical and scientific judgement must be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

The following medical conditions will be automatically regarded as serious, regardless of the classification assigned by the clinical trial Investigator reporting the case:

- Anaphylaxis or anaphylactoid reaction
- Myocardial infarction
- Stroke
- Pulmonary embolism
- Infection with any blood borne virus
- Any transmissible spongiform encephalopathy
- Development of inhibitors to IMP

In general, information that might materially affect the risk-benefit assessment of a medicinal product or that would suggest changes in the way it is to be administered or to the way a clinical investigation should be conducted should be reported in an expedited manner. Examples include:

- Single case reports of an expected adverse reaction with an unexpected outcome e.g. fatal outcome
- For an expected serious adverse reaction, an increase in the rate of occurrence which is judged to be clinically important.
- A significant hazard to the patient population, such as lack of efficacy in treating life-threatening diseases or an event which is significant enough to lead to important changes in the way a medicine is developed e.g. change in dose, monitoring, consent forms.
- A major new safety finding from a newly completed animal study.
- A serious adverse event associated with a study procedure that could modify the conduct of the trial.

1.4 Unexpected ADRs

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product). Reports which add significant information on specificity, severity or frequency about a listed ADR would be classed as 'unexpected', for example, a report of interstitial nephritis when acute renal failure is the listed ADR or a report of fulminant hepatitis when the product information only lists hepatitis.

Expectedness will be assessed against the SmPC.

1.5 Suspected Unexpected Serious Adverse Reactions (SUSARs)

All suspected adverse reactions related to an IMP (the tested IMP, comparators or placebo) which occur that are both unexpected and serious (SUSARs) are subject to expedited reporting. BPL and/or the Designated CRO (as stated in the Safety Management Plan) will be responsible for reporting these to the concerned competent authorities and to the Ethics Committee concerned, as detailed in the Safety Management Plan.

2. DETECTING ADVERSE EVENTS

Subjects will be carefully monitored for adverse events that occur after the Informed Consent Form (ICF) has been signed until the last day of the study. The Investigator or delegate will question the subjects about adverse events using a non-leading question such as "How are you feeling?" The Investigator will also record adverse events reported spontaneously by the subjects. Clinically significant changes in the findings of physical examination, and clinically significant abnormalities in the result of objective tests (e.g. laboratory variables, ECG) may also be recorded as AEs. The Investigator will use the following criteria when deciding whether to report an abnormal result as an adverse event:

1. The test result is associated with accompanying symptoms.
2. Results of additional diagnostic tests cause concern or necessitate medical intervention.
3. As a consequence of the test result, the dose administered to the subject is changed, the subject is withdrawn, or the subject is given concomitant treatment.
4. The Investigator considers the result to constitute an AE.

If any of the above criteria are met, the Investigator will report the results as an AE.

2.1 Causality

All AEs will be recorded in the CRF/e-CRF, whether considered to be related or unrelated to the treatment. The record will include the following: brief description of event (preferably a diagnosis), date and time started and stopped, severity, outcome, actions taken and classification of the AE. The Investigator should also evaluate the probability of

a causal relationship of the AE to the study medication according to the following criteria as:

1. Unrelated – Clinical event with an incompatible time relationship to IMP administration, or that could be explained by underlying disease or other drugs or chemicals, or is incontrovertibly not related to the IMP.

2. Unlikely - Clinical event whose time relationship to IMP administration makes a causal connection improbable, but that could plausibly be explained by underlying disease or other drugs or chemicals.

3. Possible - Clinical event with a reasonable time relationship to IMP administration, but that could also be explained by concurrent disease or other drugs or chemicals.

4. Probable - Clinical event with a reasonable time relationship to IMP administration, and is unlikely to be attributed to concurrent disease or other drugs or chemicals.

5. Very likely / certain – Clinical event with plausible time relationship to IMP administration, and that cannot be explained by concurrent disease or other drugs or chemicals.

Study medication is defined as those investigational compounds or their controls used in a study.

It will be assumed that for all adverse events classified as “probably related”, “possibly related” or “very likely / certainly related” to the study medication, there is reasonable likelihood that the adverse event was causally related to the product. All such adverse events will be regarded as “causally related” to the study medication.

2.2 Outcome of AEs

The outcome of the AE should be documented as:

1. Recovered / resolved
2. Recovering / resolving
3. Not recovered / not resolved
4. Recovered / resolved with sequelae

5. Fatal
6. Unknown

2.3 Action taken

The action taken by the Investigator or study staff should be documented as:

1. Drug withdrawn
2. Dose reduced
3. Dose increased
4. Dose not changed
5. Unknown
6. Not applicable

2.4 Severity of AE

Severity refers to the grading of adverse events to assess the severity of symptoms as evaluated by the investigator or as experienced by the subject. The severity grading is independent of seriousness; in other words, a severe event is not necessarily serious.

The investigator will make an assessment of severity (e.g. mild, moderate or severe) for each AE and SAE reported during the study in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) criteria (version 4.03: June 14, 2010).

The severity of the AE will be assessed by the Investigator, based on their clinical judgement and documented as:

1. Mild – No limitation to normal activities
2. Moderate – Some limitation to normal activities
3. Severe – Inability to carry out normal activities

3. ADVERSE EVENT FOLLOW UP

All adverse events will be followed:

- to resolution

  or
- until an underlying condition has been diagnosed

  or

- until the patient's condition has stabilised
  or
- for a period of 28 days following the last administration of the study drug or the last study visit, whichever is soonest.

Any new or unresolved AEs noted at the last study visit will be followed up for a further 28
days unless they fulfil the above criteria.

All pregnancies will be followed up until birth and any birth defects will be reported as in the procedures for SAEs (see section 3 and 4).

If the subject becomes pregnant while participating in the study, the pregnancy will not be recorded as an SAE, but will be captured on a Pregnancy Report Form and followed through until delivery or elective/spontaneous termination.

4. REPORTING SERIOUS ADVERSE EVENTS

When an Adverse Event occurs which fulfils the definition of serious (see Section 1.3 for definition) the Investigator must:

Complete and sign the serious adverse event form and send it within 24 hours to the appropriate person as detailed in the Safety Management Plan.

Medical cover for urgent queries relating to adverse events will be provided on a 24 hours / 7 days a week basis by the following CRO Pharmacovigilance Department INC Contact:

Address: The Meadows Business Park, Blackwater
Camberley Surrey, GU17 9AB, United Kingdom
Email: INCdrugsafety@INCResearch.com
Fax: +1-877-464-7787 or to the dedicated fax number indicated on the SAE Fax Cover Page

The Investigator is responsible for expedited reporting of all Serious Adverse Events immediately to BPL and/or the designated CRO (as stated in the Safety Management Plan)

except for those that the protocol or Investigator's Brochure identifies as not requiring immediate reporting. This reporting requirement covers any serious adverse events that develop at any point between the date when a subject provides informed consent and up to 28 days after the last administration of the investigational medicinal product. The Investigator is also responsible for reporting to BPL and/or the designated CRO (as stated in the Safety Management Plan) any serious adverse events with an onset date more than 28 days after the last administration of the product if he/she judges the serious adverse event to be possibly, probably or very likely/certainly related to the product.

The immediate report should contain the following as a minimum:

1. A suspected investigational medicinal product
2. Study subject number
3. Details of the serious adverse event
4. Classification of SAE
5. Causality of SAE (if available)

The immediate SAE form should be followed by a detailed, complete SAE form as soon as possible. The immediate report and follow-up reports shall identify subjects by unique code numbers assigned to the latter.

Adverse Events and/or laboratory abnormalities identified in the protocol as critical to the evaluation of safety must be reported to BPL and/or the designated CRO (as stated in the Safety Management Plan) by the Investigator according to the reporting requirements within the time periods specified in this protocol.

The investigator must not wait to receive additional information to document fully the event before notification of a SAE, though additional information may be requested. Where applicable, information from relevant laboratory results, hospital case records and autopsy reports should be obtained.

Instances of death, congenital abnormality or an event that is of such clinical concern as to influence the overall assessment of safety, if brought to the attention of the investigator at any time after cessation of IMP administration and linked by the investigator to this study should be reported to BPL or the designated CRO (as stated in the Safety Management Plan).

BPL and / or the designated CRO will promptly notify all relevant investigators and the regulatory authorities of findings that could adversely affect the safety of patients, affect the conduct of the study or alter the IEC/IRB approval/favorable opinion of the study. In addition, the sponsor (or designated CRO), will expedite the reporting to all concerned investigators, to the IECs/IRBs, where required, and to the regulatory authorities of all adverse events that are serious, unexpected, and in the opinion of the investigator, related to the IMP.

The investigator will comply with local requirements related to the reporting of SAEs, IND Safety Notification Letters, and other safety information related to the trial to their local IRB.

For reported deaths of a subject, the Investigator shall supply BPL and /or the designated CRO (as stated in the Safety Management Plan) and the Research Ethics Committee with any additional information requested.

Completing Serious Adverse Event Forms

Serious Adverse Event (SAE) forms must be completed in a timely manner and contain the following information:

- subject number, sex, date of birth, study centre, trial code,
- description of event (where possible a diagnosis should be made rather than just listing symptoms),
- study drug, indication for use, batch number, dose, route, date and time of last dose,
- date and time of adverse event,
- **all** concomitant medication (copy of concomitant medication page can be appended),
- causal relationship to study medication (as in Section 2.2),
- outcome (as in Section 2.3),
- action taken and treatment given (as in Section 2.4),
- severity (as in Section 2.5),
- classification of serious adverse event (as in Section 1.3),

The SAE form must be signed and dated by the person reporting the SAE. The final report must be signed and dated by the Principal Investigator from the site.

5. BPL'S RESPONSIBILITIES

BPL and/or the designated Contract Research Organisation (as stated in the Safety Management Plan) will be responsible for reporting all relevant safety information (including a listing of all SUSARs) to the competent authorities and to the Independent Ethics Committee (IEC) / Institutional Review Board (IRB) concerned. In the case of blinded studies the IEC / IRB and Competent Authority will be provided with an unblinded listing and in order not to bias the study the listing will be provided by an independent person. Safety reports will be issued in accordance with local relevant procedures (as a minimum on an annual basis).

BPL and/or the designated CRO (as stated in the Safety Management Plan) will inform the relevant competent authority (ies) in line with regulatory guidelines on adverse events occurring during the trial. The Investigator retains the right to inform the relevant competent authority(ies) if he/she so desires but must inform BPL and/or the designated CRO (as stated in the Safety Management Plan) so that duplicate reports to the competent authority(ies) can be highlighted.

BPL and/or the designated CRO (as stated in the Safety Management Plan) will inform all Investigators of all suspected unexpected serious adverse reactions occurring during the study or findings that could adversely affect the safety of subjects.

APPENDIX II - ADMINISTRATIVE REQUIREMENTS

ABBREVIATIONS AND DEFINITIONS

ARSAC	- Administration of Radioactive Substances Committee
BPL	- Bio Products Laboratory Limited
CA	- Competent Authority
CI	- Chief Investigator
COI	- Coordinating Investigator
CRA	- Clinical Research Associate
CRF	- Case Record Form
e-CRF	- Electronic Case Record Form
CV	- Curriculum Vitae
DQF	- Data Query Form
EU	- European Union
FDA	- Food and Drug Administration
GCP	- Good Clinical Practice
GMC	- General Medical Council
ICH	- International Conference on Harmonisation
ID	- Identification
IEC	- Independent Ethics Committee
IMP	- Investigational Medicinal Product
IRB	- Institutional Review Board
PI	- Principal Investigator
R&D	- Research and Development
SOP	- Standard Operating Procedure

CA – 'Competent Authority', synonymous with 'Regulatory Authority': the Government body that has the power to regulate. In the context of ICH GCP, the term 'Competent Authority' includes the authorities that review submitted clinical data and those that conduct inspections.

CI – 'Chief Investigator': in relation to a clinical trial conducted at a single trial site, the Investigator for that site. In relation to a clinical trial conducted at more than one trial site, the authorised health care professional, whether or not

he/she is an Investigator at any particular site, who takes primary responsibility for the conduct of the trial.

COI – 'Coordinating Investigator': an investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicentre trial.

PI - 'Principal Investigator': a doctor or person following a profession for investigations because of the scientific background and the experience in subject care it requires. The Principal Investigator is responsible for the conduct of the trial at the trial site. If a trial is conducted by a team of individuals at a trial site, the Principal Investigator is the leader responsible for the team.

IEC – 'Independent Ethics Committee': a review board or a committee, institutional, regional, national or supranational, constituted of medical/scientific professionals and non-medical/non-scientific members, whose responsibility it is to ensure the protection of the rights, safety and well being of human subjects involved in a clinical trial and to provide public assurance of that protection, by, among other things, reviewing and approving / providing favourable opinion on, the trial protocol, the suitability of the Investigator(s), facilities and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

IRB – 'Institutional Review Board': an independent body constituted of medical, scientific and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well being of human subjects involved in a clinical trial by, among other things, reviewing, approving and providing continuing review of the trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

IMP – 'Investigational Medicinal Product': a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled in a way different from the authorised form, or when used for an

unauthorised indication, or when used to gain further information about the authorised form.

1. ETHICAL CONSIDERATIONS

The study will be performed in accordance with the guidelines of the Declaration of Helsinki on biomedical research involving human subjects and in accordance with GCP guidelines (ICH), EU Directives 2001/20/EC[1] and 2005/28/EC[2] and FDA's Code of Federal Regulations (CFR)[3] as well as the demands of national drug and data protection laws, other applicable regulatory requirements and any new directives or regulations which become enforceable during the course of the study.

Before the study can begin the Investigator must have submitted to an Independent Ethics Committee (IEC) / Institutional Review Board (IRB) the study protocol, Investigator's Brochure, subject information leaflet, consent form (and any updates), subject recruitment procedures and any other relevant study documentation as outlined in the guidance document ('Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use', ENTR/CT 2) for EU Directive 2001/20/EC[1]. Written approval of the study must be obtained before the study centre can be initiated or the investigational medicinal product (IMP) can be released to the Investigator. Any necessary extensions or renewals of IEC / IRB approval must be obtained, in particular, for changes to the study such as modification of the protocol, the informed consent form, the written information provided to subjects and/or other procedures.

The Investigator will report promptly to the IEC / IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. The Investigator will submit written summaries of the study status to the IEC / IRB annually, or more frequently if requested by the IEC / IRB, in accordance with local regulatory requirements. On completion of the study, the sponsor will notify the IEC / IRB that the study has ended.

2. INFORMED CONSENT

No study-related procedures will be performed prior to the subject's and subject's parent/legal guardian's (if applicable) signed consent to participate in the study being obtained. Before the decision to participate, the Investigator or a duly authorised deputy will provide both an oral and a written full explanation of the study and the subject's rights. The written consent must be given by the subject and the parent/legal guardian (if applicable) of the subject, after detailed information about the study has been given as outlined above in EU Directive 2001/20/EC[1] and in accordance with any national provisions on the protection of clinical study subjects. The verbal explanation will cover all the elements specified in the written information provided for the subject.

For subjects not qualified to give legal consent, written consent must be obtained from the subject's parent/legal guardian. If appropriate, children old enough to understand the risks and benefits of the study (generally for children above 6 years of age) should also be informed and provide their written assent. In addition, the subject/subject's parent or legal guardian will sign a consent and child's assent form authorizing release of the subject's HIV test results to appropriate authorities. All consent and assent forms must be approved in advance by the IRB/IEC.

If the legal guardian is unable to read, an impartial witness should be present during the entire informed consent discussion. After the informed consent form and any other written information is provided, read, and explained to the subject or their legal guardian, and after oral consent has been obtained, if capable of doing so, the subject's legal guardian should sign and date the informed consent form, and where appropriate written assent should be obtained from the subject. The witness should also sign and date the consent form. In addition, the subject's legal guardian should, if possible, sign an additional form confirming that the materials provided have been read and explained to them. The witness should also sign and date this additional form.

The Investigator or designated personnel will inform the subject of the objectives, methods, anticipated benefits and potential risks and inconveniences of the study. The subject and parent/legal guardian (if applicable) must be given every opportunity to clarify any points they do not understand and, if necessary, to ask for more information. At the end of the interview, the subject and parent/legal guardian (if

applicable) will be given time to consider the study if this is required, or if they request more time. Subjects and parents/legal guardians (if applicable) will be required to sign and date the informed consent form. After signatures are obtained, the informed consent forms will be kept and archived by the Investigator in the Investigator's study file for possible inspection by regulatory authorities, the IEC or IRB, BPL or BPL's representative's personnel, auditors. The subject will keep an identical signed copy. A letter will be sent to the subject's primary care physician informing him/her that the subject is to participate in the study, as appropriate.

It should be emphasized to the subject that he/she is at liberty to withdraw from the study at any time, without penalty or loss of benefits to which the subject is otherwise entitled. Subjects who withdraw consent should not continue in the study, but will be asked to attend an End-of-Study visit, if possible.

Should the study require the completion of subject diary cards, for subjects under the age of consent, the parent/legal guardian will oversee that the diary is completed accurately and legibly.

The IEC / IRB will review and approve the subject information sheet and informed consent form. If the Investigator intends to use his/her own information leaflet (for non-interventional studies only) he/she must ensure that it contains all the information outlined in Section 4.8 of the ICH-GCP guidelines.

3. CONFIDENTIALITY

The investigator will ensure that the subject's anonymity is preserved.

In order to protect the subject's identity, identification codes will be used in lieu of subject's name. Personal information will be treated as confidential but may need to be reviewed by BPL or BPL's representatives such as the CRA or auditor, or by representatives of IEC / IRBs or regulatory authorities. The subject's consent to direct access to their personal notes must be obtained prior to participation in the trial. Each subject's Primary Care Physician will be informed of the nature and timing of the study, as appropriate.

All unpublished documents including the protocol, the case record form (CRF) and the Investigator's Brochure are confidential. Those documents cannot be disclosed to a

third party without the written consent of BPL. However, submission of those documents to the IEC / IRB is expressly permitted.

4. COMPENSATION/INDEMNITY

Compensation will be paid by BPL according to the Guidelines drawn up by the Association of the British Pharmaceutical Industry if a subject is injured as a result of being in this study.

Compensation will not be provided for injury or medical conditions that are unrelated to this study.

BPL will indemnify the Institute and the Investigator with respect to any claim for personal injury or death brought against it resulting from the administration to subjects, of source materials supplied by BPL, provided that the protocol and Investigator Agreement have been adhered to, and the event has not been occasioned by malpractice or negligence. BPL will take out private insurance in respect of its potential liability.

5. PROTOCOL ADHERENCE

Adherence to the protocol is a fundamental part of the conduct of the study. Deviations from the protocol, including deviations from the inclusion / exclusion criteria, might erode the scientific and ethical value of the protocol and its authorization and might have an impact on the processes put in place for the care and safety of the study subjects.

Deviations from the protocol must not be made without the **prior written approval** of BPL and the IEC / IRB and the CA except where there are logistical or administrative changes (non-substantial amendments), or where they are implemented to eliminate an immediate threat or hazard to health or safety of the subject. Where a deviation has been made to eliminate an immediate hazard the Investigator must submit a report of the implemented deviation and the reasons for it to the IEC / IRB and must notify relevant members of the **Medical Department of BPL or the designated Contract Research Organisation**. All deviations must be adequately documented.

6. PROTOCOL AMENDMENTS

A decision will first be made by BPL as to whether a protocol amendment is 'Substantial' or 'Non-substantial'. Amendments to the protocol are regarded as 'Substantial' where they are likely to have significant impact on:

- the safety or physical or mental integrity of the subjects;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any investigational medicinal product (IMP) used in the trial.

Competent Authority (CA) and IEC / IRB written approval (if applicable) will be obtained prior to any protocol amendment being adopted.

When a sponsor and/or Investigator must take urgent safety measures to protect the trial subjects from immediate hazard BPL or the designated CRO must be notified within 24 hours and the IEC / IRB and CA must be notified within 3 calendar days after appropriate safety measures have been taken. For any period during which a disease is pandemic and is a serious risk to human health or potentially a serious risk to human health, the IEC/IRB and CA should be informed as soon as possible. Where the amendment affects the risk/benefit ratio of continued participation for subjects already enrolled in the study, informed consent should be obtained again from such subjects using the new information leaflet/consent form. The updated version of the information leaflet/consent form should be used for all new subjects recruited on to the trial.

7. SERIOUS BREACHES

A Serious Breach is a breach which effects to a significant degree either the safety or physical or mental integrity of the subjects in the clinical trial or the scientific value of the clinical trial. The Investigator or participating laboratory must notify BPL or the designated Contract Research Organisation promptly (within 24 hours) of becoming aware of any Serious Breaches of the conditions and principles of GCP or the clinical trial protocol and any protocol amendment(s). BPL (or designated Contract Research Organisation) will be responsible for informing the CA and IEC / IRB of any Serious Breach in line with applicable national laws and regulations.

8. TRIAL TERMINATION

BPL reserve the right to stop the trial if:

- Recruitment is too slow to allow accrual of an adequate number of subjects within a reasonable length of time.
- Evidence is gained that the subjects are being exposed to an unacceptable risk.
- For any reason, it is not possible to continue to supply trial material.
- An advancement in knowledge makes the trial redundant.

If the study is terminated, BPL, the CRO and the investigator will ensure that adequate consideration is given to the protection of the subjects' interests.

9. MONITORING VISITS

The BPL Clinical Research Associate (CRA) or representative CRA will monitor the study by telephone, correspondence, and regular visits to the investigational sites. In accordance with
ICH-GCP guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the CRF are accurate, to carry out drug accountability and to ensure all documentation and study procedures comply with the protocol and with ICH-GCP. The frequency of monitoring visits will be determined by the rate of subject recruitment.

The CRA will ensure that:

- the facilities remain adequate
- the Investigator adheres to the protocol and ethical responsibilities
- source documents are legible and agree with entries in the CRF
- adverse events are adequately documented and reported
- investigational medicinal product is properly stored and accountability is being maintained
- laboratory samples are identified, handled and stored appropriately.

The Investigator must permit the CRA, the IEC / IRB, BPL appointed auditors and representatives from regulatory authorities direct access to all study-related documents

and pertinent hospital or medical records for confirmation of data contained within the CRFs. The Investigator will agree to make himself/herself available to correct or discuss any discrepancies. Subject confidentiality will be protected at all times.

A "Site Delegation List and Signature Log" will be completed and signed by the responsible investigator. In accordance with this authority log, study site staff (e.g. co-investigators and nurses) will be authorized to enter data into the CRF/eCRF. The monitor will visit the study centres as required.

10. AUDIT/INSPECTION

Access to documentation and facilities used during the study may be required by BPL appointed auditors or by regulatory authorities.

In the event that the regulatory authorities schedule an audit the Investigator must notify BPL immediately. BPL will in turn notify the Investigator if they are informed of an audit at an Investigator's site.

The main purposes of an audit or inspection are to confirm that the rights and welfare of the subjects have been adequately protected, and that all data relevant for the assessment of safety and effectiveness of the investigational product have been reported to the sponsor.

The verification of the CRF/e-CRF data may be performed by direct inspection of source documents, after the investigator has protected all confidential personal subject information not related to the study, in accord with local regulations.

11. REQUIRED PRE-STUDY DOCUMENTATION

Before the start of the study, BPL will require, as a minimum, the following documentation:

1. A signed copy of the protocol and signed amendments approved by the IEC/IRB.
2. A signed Clinical Trial Agreement, including any host R&D approval.
3. Other signed financial agreements (e.g. laboratory, pharmacy).

4. Signed Confidentiality Agreements for study team.

5. A signed Secrecy Agreement (if applicable).

6. A completed Investigator Financial Disclosure / Certification Statement and a Statement of Investigator (Form FDA 1572), if applicable.

7. An Indemnity Form signed and dated by both parties unless indemnity is covered by other signed agreements for the study.

8. Insurance policy or statement that this is not required.

9. IEC / IRB written approval.

10. Assurance that the IEC / IRB is organised and operates according to GCP and the applicable laws and regulations.

11. ARSAC approval (if applicable).

12. CA Approval.

13. Signed CVs of Investigators and sub-Investigators showing current position and GMC registration number, as appropriate.

14. Normal Ranges for:

- Laboratory parameters.
- Medical or technical procedures.
- Tests included in the protocol.

15. Evidence of validation of procedures/tests to be performed e.g.:

- Accreditation
- Certification
- SOPs for specialised tests

16. IEC / IRB approved subject information sheet and consent forms, identified with version number and date, plus any other written information given to subjects.

17. Investigator's Brochure, the edition clearly identified plus any updates.

18. Master randomisation list (if appropriate).

19. Decoding procedures for blinded trials.

20. Sample case record form.

If any of these documents are issued in a language other than English then verified translations are required.

12. COMPLETION AND RETURN OF CASE RECORD FORMS AND DATA QUERY FORMS

12.1 Recording Data in Case Record Forms (CRFs/eCRFs) and Data Query Forms (DQFs)

All study data will be recorded on CRFs provided by BPL or the designated Contract Research Organisation. These must be completed by the Investigator or a duly authorized assistant.

Paper CRF (if applicable)

Detailed instructions on how to complete the CRF can be found at the beginning of the CRF. Case record forms must be completed in a legible manner with a **black** ballpoint pen. **Entries made in pencil, coloured ink or with a felt tip pen are not acceptable.** Entries should be made promptly. Where data is absent, appropriate abbreviations should be entered instead of leaving blank fields.

For example, where problems arise with body fluid samples the following abbreviations may be entered:

- H = Haemolysed
- BC = Broken container

Error Correction

- Errors should be corrected by drawing a single black line through the entry without obscuring the original data.
- Correction should be recorded beside it and should be signed, dated and an explanation given (if necessary).
- Tippex should **never** be used.

Electronic CRF (if applicable)

In the case of an e-CRF, errors occurring in the e-CRFs will be corrected directly in the data field of the e-CRF. An audit trail capturing the original entry, the new entry, the user ID of the entry personnel, and the date and time of each action will be maintained in the data capture system. Likewise, the interchange of queries between the CRO and the site, as well as query replies, will be maintained within the audit trail of the data capture system. Any changes to the data in the data capture system that occur after the investigator or authorised co-investigator have electronically signed the e-CRF will

require that the investigator or authorised co-investigator review and re-sign the e-CRF.

12.2 Signing off CRFs/DQFs and return to BPL or the designated Contract Research Organisation

The Investigator must:

- Sign the completed CRF/DQFs to confirm the validity of the data.
- Return the completed CRF/DQFs as instructed.
- Retain a copy in the Investigator File.

In the case of e-CRFs for each subject enrolled, e-CRFs will be completed and signed electronically by the investigator or an authorised co-investigator. All paper source documents will be filled out using an indelible pen, and must be legible.

12.3 Handling of clinical trial data

All clinical trial data will be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, whilst maintaining the confidentiality of the subjects' records.

12.4 Source Documents

Source documents or data to be entered directly into the Case Record Form will be defined prior to study start in an appropriate plan e.g. definition of source data document.

Source data are defined as all information related to clinical findings, observations, or other activities in the study, written in original records or consisting of certified copies of original records. The investigator will permit trial-related monitoring, audit(s), IRB review(s) and regulatory inspection(s).

13. MAINTENANCE AND ARCHIVING OF STUDY RECORDS

13.1 Investigator Site File

The Investigator will be supplied with an Investigator Site File by BPL or the designated Contract Research Organisation at the start of the study, containing copies of required pre-study essential documents. It is the responsibility of the Investigator and study team members at site to maintain these essential documents and ensure their secure storage. The Investigator Site File will comprise the following documentation, although certain sections may be kept in a separate file with certain study team members e.g. laboratory or pharmacy staff:

1. Agreements

- Signed Confidentiality Agreements for study team.
- Signed Clinical Trial Agreement, including any host R&D approval (and submission documentation where applicable) detailing versions of the documents approved.
- .
- Other signed financial agreements specific to the site (e.g. laboratory, pharmacy).
- Indemnity Form (if used) signed and dated by both parties, unless indemnity is covered by other signed agreements for the study.
- Insurance statement if applicable

A completed Investigator Financial Disclosure / Certification Statement and a Statement of Investigator (Form FDA 1572), if applicable.

2. Protocol

A signed copy of the protocol and signed amendments approved by the IEC/IRB.

3. Product Information

- Investigator's Brochure, the edition clearly identified plus any updates.
- Supporting publications and information.
- Safety updates from BPL, including any aggregated line listings of SUSARs and summary safety reports, in accordance with local regulatory requirements.

4. CRF/eCRF and Supporting Information

- Sample case record form.
- Other blank forms used in the study e.g. diary cards.

Data transmittal forms.

5. CVs

- Signed CVs of Investigators and sub-Investigators showing current position and GMC registration number, as appropriate.
- Site Delegation of Duties Log.
- Reference to training records of study site personnel/ Site training log.

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6. Ethics Committee

- IEC / IRB written approval.
- CA Approval.
- ARSAC approval (if applicable).
- Relevant correspondence with IEC/IRB.
- Copies of progress reports to IEC/IRB.
- Copies of annual safety reports to IEC/IRB, in accordance with local regulatory requirements.
- Copies of IEC/IRB approved consent forms.
- Copies of IEC/IRB approved information leaflets.
- Final letter and report to IEC/IRB documenting study completion.

7. Laboratory Details

- Central laboratory manual, if applicable
- Local laboratory normal ranges both current and previous if changed during study, if applicable.
- Local laboratory certification / accreditation both current and any updates.
- Local laboratory validation or SOPs for specialized tests both current and any updates.
- Sample storage log.
- Local sample handling procedures, unless included in a central laboratory manual

- Laboratory parameters
- Medical or technical procedures
- Tests included in the protocol.

8. Subject Details

- Master randomization list (if appropriate).
- Subject screening log (if appropriate).
- Subject enrolment log (if appropriate).
- Signed informed consent forms; informed consent checklist, if used.
- Template of letter to primary physician.

Completed subject identification code list for randomized studies (at study completion).

9. Adverse Events

- Reports of Serious Adverse Events and SUSARs.
- Correspondence relating to SAEs and SUSARs.
- Notification of SUSARs to IEC/IRB.

10. General Correspondence

11. Investigational Medicinal Product

- IMP receipt forms.
- Procedure for temperature monitoring
- Certificates of Analysis, if requested
- IMP accountability records.
- Instructions for handling IMP.
- Example prescription form (if applicable).
- Documentation of destruction of IMP.
- Randomisation code location (if not kept in Investigator Site File).

12. Monitoring

- Pre-study and Initiation Site Visit Report forms.
- Case Record Form correction notes.

Data query forms.

13. Reports

- Any interim clinical study report.

The final Clinical Study Report. A synopsis will suffice.

14. Completed CRFs

- Copies of completed CRFs or reference if stored separately.
- Copy of any CRF and data query tracking and acknowledgement forms.

15. Meetings

- Minutes of meetings, agenda and correspondence relating to meetings.

16. Publications

- Any publications of trial results available before site closure.

If any of these documents are issued in a language other than English then verified translations are required.

13.2 Subject notes

The Investigator must maintain adequate records of subject participation for the duration of the study. These records must be available for inspection upon reasonable request by the sponsor, members of the regulatory authorities or other authorized individuals. The Investigator must detail in the subject notes that the subject is eligible for the study prior to enrolment. The Investigator must also ensure that worksheets provided for the study that form part of the source data must always be included in the subject notes.

13.3 Availability of data for inspection

The Investigator is obliged to provide BPL, or BPL's representative, with complete test results and all data and reports within the timeframe agreed by both parties.

After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file. This file will be available for inspection by the sponsor or its representatives.

13.4 Archiving study documentation

The Investigator must make proper provision for archiving study documentation. Essential documents must be retained in accordance with ICH-GCP. Essential documents must be retained for two years after the last marketing approval in an ICH region or until at least two years have elapsed since the discontinuation of clinical development of the IMP. It is BPL's responsibility to inform the Investigator or Institute as to when these documents no longer need to be retained. It is the Investigator's responsibility to notify BPL, or BPL's representative, in writing if they are unable to make suitable provisions for archiving study documents at the study centre. Prior to archive, subject ID codes should be kept in a suitable place to enable easy access at the Investigator site. Subject ID codes must be retained for a period of at least 15 years after issue of the final study report. Subject consent forms and other study related documentation must be retained for a maximum period of time permitted by the hospital, institution or private practice

Essential documents from trials which are not to be used in regulatory submissions should be retained for at least five years after completion of the trial. These documents should be retained for a longer period if required by the applicable regulatory requirements or by agreement with BPL.

No study document should be destroyed without prior written agreement between the investigator and the sponsor. Should the investigator elect to assign the study documents to another party, or move them to another location, the sponsor must be notified.

14. REPORT AND PUBLICATION

In accordance with relevant guidelines, a final clinical study report will be prepared after the completion of the study.

BPL's standard report and publication policy is detailed below. In the case of the agreement between BPL and the Investigator differing from this policy, what is stated in the agreement will override what is stated below.

BPL recognizes that the Investigator might wish to publish the results of the study. The Investigator and members of the Investigator's team engaged in the study shall not be permitted to present at symposia and professional meetings or to publish journals, theses or dissertations, or otherwise of their choosing, methods and results of the Study (all of which hereinafter referred to as "the Publication") without the consent of BPL.

In the case that the Investigator or members of the Investigator's team engaged in the study wish to pursue the Publication, the Investigator shall furnish BPL with copies of the Publication at least two months in advance of the intended date of whichever is the earliest submission of the Publication or presentation of the Publication or publication of the Publication or the making of a commitment to do any of the foregoing. The Investigator agrees, if BPL requests a meeting between the Investigator and BPL, to discuss in good faith the comments.

BPL shall have two months, after receipt of said copies, to object to such proposed Publication on reasonable grounds. For the avoidance of doubt the grounds that the subject matter is patentable or commercially sensitive shall constitute reasonable grounds.

Authorship should reflect work done by the investigators and BPL personnel, in accordance with generally recognised principles of scientific collaboration.

15. REFERENCES

1. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

2. Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorization of the manufacturing or importation of such products.

3. FDA guidelines CFR 21 (ww.w.fda.gov) which dictates the regulations and principles for conducting clinical trials in the USA, detailed guidelines are also provided.

APPENDIX III – GUIDELINES ON THE MAXIMUM VOLUME OF BLOOD WHICH CAN BE WITHDRAWN FROM CHILDREN ACCORDING TO BODY WEIGHT

Working on 1 mL per kg allowed in 24 hrs

Boys				Girls			
Age (years)	**50th percentile weight (kg)[1]**	**maximum blood volume in 24 hrs**	**maximum blood volume in 1 month[2]**	**Age (years)**	**50th percentile weight (kg)[1]**	**maximum blood volume in 24 hrs**	**maximum blood volume in 1 month[2]**
0	3.5	3.5	14.1	0	3.4	3.4	13.6
0.5	8.2	8.2	32.7	0.5	7.5	7.5	29.8
1	10.5	10.5	41.8	1	9.7	9.7	38.7
1.5	11.8	11.8	47.2	1.5	11.1	11.1	44.4
2	12.7	12.7	50.7	2	12.1	12.1	48.2
3	14.4	14.4	57.6	3	13.9	13.9	55.8
4	16.3	16.3	65.3	4	15.9	15.9	63.5
5	18.5	18.5	73.9	5	18.0	18.0	72.1
6	20.8	20.8	83.1	6	20.3	20.3	81.3
7	23.2	23.2	92.7	7	22.9	22.9	91.5
8	25.8	25.8	103.0	8	25.8	25.8	103.0
9	28.7	28.7	114.7	9	29.1	29.1	116.6
10	32.1	32.1	128.4	10	33.1	33.1	132.3
11	36.1	36.1	144.3	11	37.4	37.4	149.6
12	40.7	40.7	162.7	12	41.8	41.8	167.3
13	45.8	45.8	183.3	13	46.0	46.0	183.9
14	51.2	51.2	204.9	14	49.5	49.5	198.0
15	56.5	56.5	226.0	15	52.1	52.1	208.5
16	61.1	61.1	244.4	16	53.9	53.9	215.8
17	64.7	64.7	258.8	17	55.2	55.2	220.7
18	67.3	67.3	269.2	18	56.2	56.2	224.9

[1] Weights are taken from the USA Centre for Disease Control and Prevention website: http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/html_charts/wtageinf.htm

[2] Four times the blood volume taken in 24 hours.

APPENDIX IV - LOCAL INVESTIGATOR'S RESPONSIBILITIES BASED ON THE GUIDELINES FOR GOOD CLINICAL PRACTICE

1. LOCAL INVESTIGATOR

1.1 Investigator's Qualifications and Agreements

1.1.1 The Investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the study, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/EC, and/or the regulatory authority(ies).

1.1.2 The Investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.

1.1.3 The Investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.

1.1.4 The Investigator should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).

1.1.5 The Investigator should maintain a list of appropriately qualified persons to whom the Investigator has delegated significant study-related duties.

1.2 Adequate Resources

1.2.1 The Investigator should be able to demonstrate (*e.g.* based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

1.2.2 The Investigator should have sufficient time to properly conduct and complete the study within the agreed study period.

1.2.3 The Investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the study to conduct the study properly and safely.

1.2.4 The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, the investigational product(s), and their study-related duties and functions.

1.3 Medical Care of Study Subjects

1.3.1 A qualified physician (or dentist, when appropriate), who is an Investigator or a sub-Investigator for the study, should be responsible for all study-related medical (or dental) decisions.

1.3.2 During and following a subject's participation in a study, the Investigator should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the study. The Investigator should inform a subject when medical care is needed for intercurrent illness(es) of which the Investigator becomes aware.

1.3.3 It is recommended that the Investigator inform the subject's primary physician about the subject's participation in the study if the subject has a primary physician and if the subject agrees to the primary physician being informed.

1.3.4 Although a subject and their Parent(s)/Guardian(s) are not obliged to give their reason(s) for withdrawing prematurely from a study, the Investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

1.4 Communication with IRB/EC

1.4.1 Before initiating a study, the Investigator should have written and dated approval/favourable opinion from the IRB/EC for the study protocol, written informed consent form, consent form updates, subject recruitment procedures (*e.g.*, advertisements), and any other written information to be provided to subjects.

1.4.2 During the study the Investigator should provide to the IRB/EC all documents subject to review.

1.5 Compliance with Protocol

1.5.1 The Investigator should conduct the study in compliance with the protocol agreed by the sponsor and, if required, by the regulatory authority (ies) and which was given approval/favourable opinion by the MREC. The Investigator and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

1.5.2 The Investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the IRB/EC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (e.g. change in monitor(s), change of telephone number(s)).

1.5.3 The Investigator, or person designated by the Investigator, should document and explain any deviation from the approved protocol.

1.5.4 The Investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to study subjects without prior IRB/EC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted.

a) to the IRB/EC for review and approval/favourable opinion,
b) to the sponsor for agreement and, if required,
a) to the regulatory authority(ies).

1.6 Investigational Product(s)

1.6.1 Responsibility for investigational product(s) accountability at the study site(s) rests with the Investigator.

1.6.2 Where allowed/required, the Investigator may/should assign some or all of the Investigator's duties for investigational product(s) accountability at the study site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the Investigator.

1.6.3 The Investigator and/or a pharmacist or other appropriate individual, who is designated by the Investigator, should maintain records of the product's delivery to the study site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and study subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

1.6.4 The investigational product(s) should be stored as specified by the sponsor and in accordance with applicable regulatory requirement(s).

1.6.5 The Investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.

1.6.6 The Investigator, or a person designated by the Investigator, should explain the correct use of the investigational product(s) to each subject/Parent(s)/Guardian(s) and should check, at intervals appropriate for the study, that each subject/Parent(s)/Guardian(s) are following the instructions properly.

1.7 Randomisation Procedures and Unblinding

The Investigator should follow the study's randomisation procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the study is blinded, the Investigator should promptly document and explain to the sponsor any premature unblinding,(*e.g.*, accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

1.8 Informed Consent of Study Subjects

1.8.1 In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the study, the Investigator should have the IRB/EC written approval/favourable opinion of the written informed consent form and any other written information to be provided to subject/Parent(s)/Guardian(s).

1.8.2 The written informed consent form and any other written information to be provided to subjects/Parent(s)/Guardian(s) should be revised whenever important new information becomes available that may be relevant to the subject's/Parent(s)/Guardian(s)' consent. Any revised written informed consent form, and written information should receive the IRB/EC approval/favourable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's/Parent(s)/Guardian(s)' willingness to continue participation in the study. The communication of this information should be documented.

1.8.3 Neither the Investigator, nor the study staff, should coerce or unduly influence a subject/Parent(s)/Guardian(s) to participate or to continue to participate in a study.

1.8.4 None of the oral and written information concerning the study, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the Investigator, the institution, the sponsor, or their agents from liability for negligence.

1.8.5 The Investigator, or a person designated by the Investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the study including the written information given approval/favourable opinion by the IRB.

1.8.6 The language used in the oral and written information about the study, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.

1.8.7 Before informed consent may be obtained, the Investigator, or a person designated by the Investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. All questions about the study should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

1.8.8 Prior to a subject's participation in the study, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

1.8.9 If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject's legally acceptable representative has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

1.8.10 Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

a) That the study involves research.

b) The purpose of the study.

c) The study treatment(s) and the probability for random assignment to each treatment.

d) The study procedures to be followed, including all invasive procedures.

e) The subject's/Parent(s)/Guardian(s)' responsibilities.

f) Those aspects of the study that are experimental.

g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, foetus, or nursing infant.

h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject/Parent(s)/Guardian(s) should be made aware of this.

i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.

j) The compensation and/or treatment available to the subject/Parent(s)/Guardian(s) in the event of study-related injury.

k) The anticipated prorated payment, if any, to the subject/Parent(s)/Guardian(s) for participating in the study.

l) The anticipated expenses, if any, to the subject/Parent(s)/Guardian(s) for participating in the study.

m) That the subject's participation in the study is voluntarily through its Parent(s)/Guardian(s) and that the subject/Parent(s)/Guardian(s) may refuse to participate or withdraw from the study, at any time, without penalty or loss of benefits to which the subject/Parent(s)/Guardian(s) are otherwise entitled.

n) That the monitor(s), the auditor(s), IRB, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorising such access.

o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the study are published, the subject's identity will remain confidential.

p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.

q) The person(s) to contact for further information regarding the study and the rights of study subjects, and whom to contact in the event of study-related injury.

r) The foreseeable circumstances and/or reasons under which the subject's participation in the study may be terminated.

s) The expected duration of the subject's participation in the study.

t) The approximate number of subjects involved in the study.

1.8.11 Prior to participation in the study, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the study, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

1.8.12 When a clinical study (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the study with the consent of the subject's legally acceptable representative (*e.g.*, minors, or patients with severe dementia), the subject should be informed about the study to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.

1.8.13 Except as described in 1.8.14, a non-therapeutic study (*i.e.* a study in which there is not anticipated direct clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

1.8.14 Non-therapeutic studies may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:

a) The objectives of the study can not be met by means of a study in subjects who can give informed consent personally.

b) The foreseeable risks to the subjects are low.

c) The negative impact on the subject's well-being is minimised and low.

d) The study is not prohibited by law.

e) The approval/favourable opinion of the IRB/EC is expressly sought on the inclusion of such subjects, and the written approval/favourable opinion covers this aspect.

Such studies, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these studies should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

1.8.15 In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favourable opinion by the IRB/EC, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the study as soon as possible and consent to continue and other consent as appropriate (see 1.8.10) should be requested.

1.9 Records and Reports

1.9.1 The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

1.9.2 Data reported on the CRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained.

1.9.3 Any change or correction to a CRF should be dated, initialled, and explained (if necessary) and should not obscure the original entry (*i.e.* an audit study should be maintained): this applies to both written and electronic changes or corrections (see 1.18.4 (n)). Sponsors should provide guidance to Investigators and/or the Investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the Investigator. The Investigator should retain records of the changes and corrections.

1.9.4 The Investigator should maintain the study documents as specified in Essential Documents for the Conduct of a Clinical Study and as required by the applicable regulatory requirement(s). The Investigator should take measures to prevent accidental or premature destruction of these documents.

1.9.5 Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the Investigator as to when these documents no longer need to be retained.

1.9.6 The financial aspects of the study should be documented in an agreement between the sponsor and the Investigator.

1.9.7 Upon request of the monitor, auditor, IRB, or regulatory authority, the Investigator should make available for direct access all requested study-related records.

1.10 Progress Reports

1.10.1 The Investigator should submit written summaries of the study status to the IRB/EC annually, or more frequently, if requested by the IRB/EC.

1.10.2 The Investigator should promptly provide written reports to the sponsor, the IRB/EC and, where applicable, the institution on any changes significantly affecting the conduct of the study, and/or increasing the risk to subjects.

1.11 Safety Reporting

1.11.1 All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (*e.g.*, Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the study subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The Investigator

should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/EC.

1.11.2 Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

1.11.3 For reported deaths, the Investigator should supply the sponsor and the IRB/EC with any additional requested information (*e.g.*, autopsy reports and terminal medical reports).

1.12 Premature Termination or Suspension of a Study

If the study is prematurely terminated or suspended for any reason, the Investigator should promptly inform the study subjects/Parent(s)/Guardian(s), should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition:

1.12.1 If the Investigator terminates or suspends a study without prior agreement of the sponsor, the Investigator should inform the institution where applicable, and the Investigator should promptly inform the sponsor and the IRB/EC, and should provide the sponsor and the IRB/EC a detailed written explanation of the termination or suspension.

1.12.2 If the sponsor terminates or suspends a study, the Investigator should promptly inform the institution where applicable and the Investigator should promptly inform the IRB/EC and provide the IRB/EC a detailed written explanation of the termination or suspension.

1.12.3 If the IRB/EC terminates or suspends its approval/favourable opinion of a study, the Investigator should inform the institution where applicable and the Investigator should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

1.13 Final Report(s) by Investigator

Upon completion of the study, the Investigator, where applicable, should inform the institution: the Investigator should provide the IRB/EC with a summary of the study's outcome, and the regulatory authority(ies) with any reports required.

APPENDIX V - RECONSTITUTION AND ADMINISTRATION INFORMATION

Optivate® may only be reconstituted with the included water for injection. The 500 IU presentation should be reconstituted using 5 mL sterilised water for injections

The containers of Optivate® and the sterilised water for injection have to be brought to a temperature between 20°C and 30°C before the removal of the flip off cap.

You can dissolve your product using the Transfer Device called Mix2Vial™:
The Mix2VialTM Transfer Device is provided with your product for needle-free, easy and safe use. The reconstitution is performed as follows:

	Step 1 •Remove the cap from the product vial and clean the top of the stopper with an alcohol swab. •Repeat this step with the sterile water vial. •Peel back the top of the Transfer Device package but leave the device in the package.
	Step 2 •Place the blue end of the Transfer Device on the water vial and push straight down until the spike penetrates the rubber stopper and snaps into place. •Remove the plastic outer packaging from the Transfer Device and discard it, taking care not to touch the exposed end of the device.
	Step 3 •Turn the water vial upside down with the device still attached. •Place the clear end of the Transfer Device on the product vial and push straight down until the spike penetrates the rubber stopper and snaps into place.
	Step 4 •The sterile water will be pulled into the product vial by the vacuum contained within it. •Gently swirl the vial to make sure the product is thoroughly mixed. Do not shake the vial. •A clear or slightly pearl-like solution should be obtained, usually in about 2 to 2 ½ minutes (5 minutes maximum).
	Step 5 •Separate the empty water vial and blue part from the clear part by unscrewing anti-clockwise. •Draw air into the syringe by pulling the plunger to the required volume of water added. •Connect the syringe to the white filter. •Push the air in the syringe into the vial.

	Step 6 •Immediately invert the vial of solution which will be drawn into the syringe. •Disconnect the filled syringe from the device. •The product is now ready for administration. Follow the normal safety practices for administration. Use the product immediately after reconstitution, the product must not be stored.

Note: If you have more than one vial to make up your dose, repeat Steps 1 through 6 withdrawing the solution in the vial into the same syringe.

The Transfer Device supplied with the product is sterile and cannot be used more than once. When the reconstitution process is complete, dispose of in the 'sharps box.

Any unused product or waste material should be disposed of in accordance with local requirements.

The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. Reconstituted products should be inspected visually for particulate matter and discolouration prior to administration. Infuse the product as soon as possible after reconstitution and certainly within one hour.

APPENDIX VI- FLOW CHART FOR 8VWF07

Exposure days (ED) to Optivate®					1 ED				10 to 15 ED				50 to 75 ED				at least 100 ED				
	Screening visit				Basline visit (V1)				V2				V3				End of Study (V4)				Safety FU
study time during optivate® treatment	minus 4 wks				0 wks				4 wks				4 months (mons)[3]				9 to 12 mons[3]				10 to 13 mons[3]
HOURS (time windows)	pre-bolus			1 ±10 mins	pre-bolus			1 ±10 mins	pre-bolus			1 ±10 mins	pre-bolus			1 ±10 mins	pre-bolus			1 ±10 mins	
MINUTES (time windows)		15 ±5 mins	30 ±5 mins			15 ±5 mins	30 ±5 mins			15 ±5 mins	30 ±5 mins			15 ±5 mins	30 ±5 mins			15 ±5 mins	30 ±5 mins		
PROCEDURE:																					
Written Informed Consent	x																				
Inclusion/Exclusion Criteria	x				x[4]																
Medical History	x																x[5]				
Physical/Medical Examination	x																x[5]				
Body weight	x				x				x				x				x				
Demographics	x																				
Concurrent Medication	x				x[2]				x[2]				x[2]				x[2]				
FVIII:C Sample	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
FVIII Inhibitor	x				x				x				x				x				
Reserve FVIII:C and FVIII inhibitor sample	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
CD4 count	x																				
Virology : Anti-HIV1, HBsAg, Anti-HCV, Anti-HAV (IgM), Anti-HAV (IgG)	x[1]				x												x				
Genotyping: gene mutation, if not already available	x																				
1mL archive serum sample stored at -70°C					x												x				
Bolus Dose (30 IU/kg)	current FVIII				Optivate®				Optivate®				Optivate®				Optivate®				
Optivate® supplied								x[7]				x[7]				x[7]					
Optivate® Drug accountability									x				x				x				x
Telephone Safety Follow-Up (FU)																					
Adverse Events and SAEs[6]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[8]
Study Diary				issued[7]	To be used throughout this period																

1) only HIV test to be conducted at screening

2) changes in concurrent mediation

3) a month is defined as 28 days

4) review screening bloods, to check eligibility

5) brief update from screening visit, including height

6) including infusions site reactions and clinically signicant changes in vital signs

7) issued after all the visit assessments have been conducted

8) only AEs via telphone