# Statistical Analysis Plan

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|---|---|
| **Sponsor Name:** | **Bio Products Laboratory Limited (BPL)** |
| **Protocol Number and Title:** | **8VWF07 – A Multicentre, Non-controlled, Prospective, Post-Marketing Safety Study Following Long-Term Prophylactic Optivate® Treatment in Subjects with Severe Haemophilia A** |
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| **Author:** | *Martin Rimmer, Principal Biostatistician* |
| **SAP Version:** | 1.0 |
| **SAP Version Date:** | 02-October-2014 |

# Statistical Analysis Plan

**Version: 1.0** **Version Date: 02-October-2014**

I confirm that I have reviewed this document and agree with the content.

| APPROVALS | |
|---|---|
| ***INC Research*** | |
| | |
| Lead Biostatistician<br>Martin Rimmer, Principal Biostatistician | **Date** (dd-Mmm-yyyy) |
| Senior Reviewing Biostatistician<br>John Williams, Senior Director, Biostatistics | **Date** (dd-Mmm-yyyy) |
| ***BPL*** | |
| | |
| Tim Aldwinckle, BPL Medical Director | **Date** (dd-Mmm-yyyy) |
| Ernie Gascoigne, BPL Head of Medical Affairs | **Date** (dd-Mmm-yyyy) |
| Miranda Norton, BPL Clinical Project Leader | **Date** (dd-Mmm-yyyy) |

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Statistical Analysis Plan

# 1. GLOSSARY OF ABBREVIATIONS

| Abbreviation | Description |
|---|---|
| AE | Adverse Event |
| ANOVA | Analysis of Variance |
| ATC | Anatomical Therapeutic Chemical |
| BPL | Bio Products Laboratory Limited |
| CD4 | Cluster Differentiation 4 |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | Confidence Interval |
| CRF | Case Report Form |
| ED | Exposure Days |
| FVIII | Factor VIII |
| HIV | Human Immunodeficiency Virus |
| ICH | International Conference on Harmonisation |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mL | Millilitre |
| PT | Preferred Term |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SmPC | Summary of Product Characteristics |
| SOC | System Organ Class |
| TEAE | Treatment Emergent Adverse Event |
| WHO | World Health Organisation |

# 2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

## 2.1. RESPONSIBILITIES

INC Research will perform the statistical analyses and are responsible for the production and quality control of all tables, figures and listings.

## 2.2. TIMINGS OF ANALYSES

The primary analysis of efficacy and safety is planned after all subjects complete the final study visit or terminate early from the study.

There is no interim analysis.

# 3. STUDY OBJECTIVES

## 3.1. PRIMARY OBJECTIVE

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

## 3.2. SECONDARY OBJECTIVE

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

# 4. STUDY DESIGN

## 4.1. BRIEF DESCRIPTION

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

At screening eligibility will be assessed. Eligible subjects will receive a bolus dose (30 IU/kg) of the subject's current FVIII for a recovery assessment.

At Baseline Visit (Visit 1), subjects eligible to continue will receive a bolus dose of Optivate® (30 IU/kg) for recovery assessments. Bolus doses (30 IU/kg) will also be administered at Visit 2, Visit 3, and Visit 4. Following Visit 1, 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.

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 Committee for Medicinal Products for Human Use (CHMP) guidelines[1].

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.

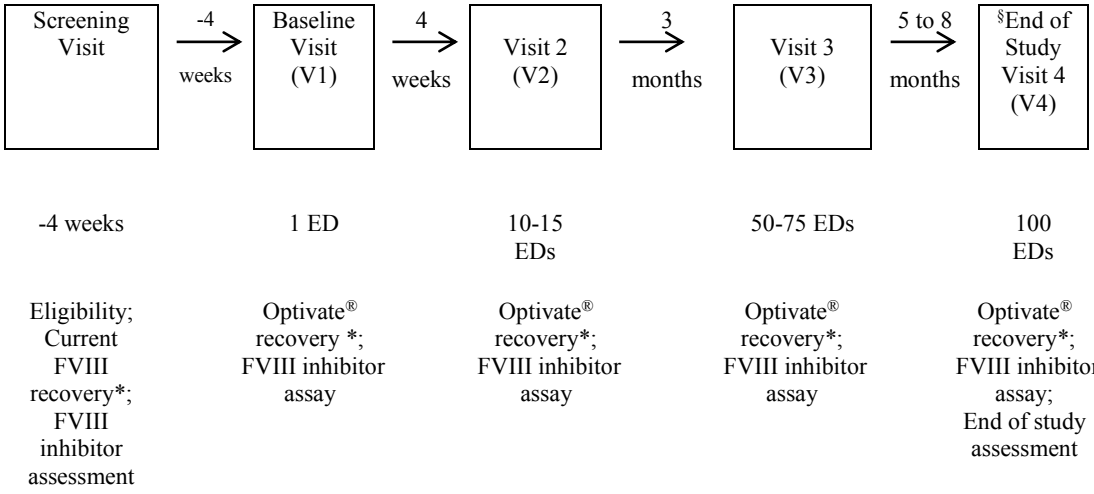
Subjects will undergo the visit schedule as shown in Figure 1. A recovery assessment will be conducted at each visit, after a 3 day washout period.

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.

The duration of the study for each subject is estimated to be no longer than 56 weeks in total, comprising of a variable screening period (approximately 4 weeks) and a treatment period of up to 12 months (52 weeks).

# Statistical Analysis Plan

**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

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.

## 4.2. SUBJECT SELECTION

### 4.2.1. 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 FVIII < 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 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.

### 4.2.2. 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) prior to administering Optivate®.
- Known or suspected hypersensitivity to the Investigational Medicinal Product or its excipients.
- Clinically significant:
    - liver disease (serum Alanine Aminotransferase levels greater than three times the upper limit of the normal range)
    - renal disease (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.

## 4.3. 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 licensing agreement for Optivate®. Therefore for this study 12 subjects will be enrolled to ensure data for 10 evaluable subjects.

## 4.4. TREATMENT ASSIGNMENT & BLINDING

This is a single arm study therefore treatment assignment and blinding are not applicable.

## 4.5. ADMINISTRATION OF STUDY MEDICATION

At Baseline Visit (Visit 1), 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 Visit 2, Visit 3, and Visit 4.

Following Visit 1, 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.

# Statistical Analysis Plan

This will be at a dose agreed with the Investigator and in accordance with the Summary of Product Characteristics (SmPC)[2] 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 (Visit 1), Visit 2, Visit 3 and End of Study Visit (Visit 4) which will be to the nearest 0.1 mL.

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 labeled with the batch number, nominal unitage, actual vial content in IU, expiry date and study code. The vial cartons will have space to enter the site details and subject number.

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 Visit 1 (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, which is printed on the vial label. The following details will be recorded in the CRF for Optivate® administered at recovery assessment:

- batch number

- actual volume infused (mL).

The following derived data will also be presented:

- actual dose given (IU)
- actual dose give (IU/kg).

## 4.6. STUDY PROCEDURES AND FLOWCHART

A detailed flowchart showing assessments to be performed is presented on the following page.

Scheduled visits include:

- Screening Visit
- Baseline Visit - Visit 1, to take place within 4 weeks of the screening visit
- Visit 2 - to take place 4 weeks after the Baseline Visit
- Visit 3 - to take place 3 months after Visit 2
- End of Study Visit - Visit 4, to take place once the subject has completed at least 100 EDs, which is estimated to occur between 9 and 12 months after the Baseline Visit.
- Safety Follow-Up (telephone contact) to take place 28 days after the last Optivate® infusion.

Note, Visits 2 and 3 are scheduled for when subjects are estimated to have reached between 10 and 15 EDs and between 50 and 75 EDs respectively. If the minimum EDs have not been reached for these visits, then the visits will be rescheduled.

# 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] | | | | 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

# 5. ENDPOINTS

## 5.1. PRIMARY EFFICACY ENDPOINT

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

## 5.2. SECONDARY EFFICACY ENDPOINTS

The secondary efficacy endpoints are:

- Recovery with current FVIII (screening Visit) versus 1st dose with Optivate® (Visit 1).
- Recovery at 1 ED (Visit 1), 10-15 EDs (Visit 2), 50-75 EDs (Visit 3) and 100 EDs (Visit 4).
- Number of break through bleeds including severity, duration, location and cause.
- Clinician's judgment of break-through bleed treatment outcome (excellent, good, moderate, poor).
- Subject's judgment 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.

## 5.3. SAFETY ENDPOINTS

The safety endpoints are:

- Viral serology.
- FVIII inhibitor (assessed as a primary efficacy endpoint).
- Physical/medical examinations.
- The number of AEs and Serious Adverse Drug Reactions as defined by ICH. Adverse drug reactions are defined as AEs which are recorded as having a possible, probable or very likely/certain causality related to Optivate®. 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®

# 6. ANALYSIS POPULATIONS

## 6.1. PER PROTOCOL POPULATION

The Per Protocol Population is defined as all subjects who have completed a minimum of 100 EDs with Optivate®. The Per Protocol Population is the primary population for the analysis of efficacy endpoints.

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

## 6.2. SAFETY POPULATION

The Safety Population is defined as all subjects who received at least part of one dose of Optivate®. The Safety Population will be used for all analyses of safety endpoints, and as a secondary population for the analysis of efficacy endpoints.

## 6.3. OTHER ANALYSIS SETS

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 ≥ 1%.

## 6.4. PROTOCOL DEVIATIONS

Protocol deviations will be identified from the deviations log compiled by the study monitors. Further deviations may be identified from the clinical database. Deviations will be identified prior to database lock, and will be listed only.

# 7. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

## 7.1. GENERAL METHODS

Statistical outputs will be generated using SAS version 9.3 (or later).

The study only has one treatment and so all summary tables will have a single results column for Optivate®. However, if subjects suffering from severe haemophilia A with basal FVIII values of < 2% rather than < 1% are recruited into the study, an additional two results columns will be presented, one for subjects with a basal FVIII < 1%, and one for subjects with a basal FVIII ≥ 1% (see Section 6.3).

Continuous variables will be summarised using the number of observations (n), mean, 95% confidence interval for the mean, standard deviation (SD), median, minimum, and maximum. 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, and SDs will be quoted to one further decimal place than the mean value. Categorical variables will be summarised using number of observations (n), frequency and percentages of subjects. Percentages will be rounded to one decimal place, with the exception of 0% and 100%, which will be presented to no decimal places.

All relevant subject data will be included in listings. All subjects entered into the database will be included in subject data listings.

Data from unscheduled visits will not be included in the summary tables. These data will be listed only.

Where multiple data/results are available at a given visit for the same parameter, the first non-missing result will be used in the summary tables. All data will however be listed.

## 7.2. KEY DEFINITIONS

Study day 1 is the day of the first dose of Optivate®. This is expected to be the date of the Baseline Visit. Study day -1 is the day prior to this.

## 7.3. MISSING DATA

All available data will be used in the statistical analysis. There will be no imputation for missing data.

## 7.4. VISIT WINDOWS

Visit windows will not be applied. All data will be summarised according to the nominal visit at which they were collected.

Subjects who withdraw from the study are to complete the End of Study/Visit 4 CRF pages. For summaries based on the Safety Population, these data will be summarised under 'End of Study'. An additional summary will also be provided for 'Visit 4', which will only include data from subjects who do not withdraw.

## 7.5. POOLING OF CENTRES

Data across all centers will be pooled for statistical analysis. Due to the small number of subjects to be recruited, center will not be included as a factor in any of the statistical models.

## 7.6. SUBGROUPS

With the exception of the possible analyses based on basal FVIII values, described in Section 6.3, no subgroup summaries are planned.

# 8. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

## 8.1. SUBJECT DISPOSITION AND WITHDRAWALS

The number of subjects screened and enrolled will be presented. The number and percentage of subjects completing treatment and withdrawing from treatment will be summarised along with the reason for withdrawal.

The number and percentage of subjects in the Safety and Per Protocol Populations will be presented.

Inclusion and exclusion criteria will be listed only.

Time on study (days) is defined as:

Time on Study (Days) = Date of Visit 4 (end of study visit)/withdrawal visit – Date of Baseline visit + 1

Time on study in months and years will also be calculated by dividing the time on study calculated in days by 28 and 365 respectively.

Time on study calculated in each of days, months and years will be summarized for the Safety Population.

Total time on study will be presented in both months and years for the Safety Population. These will be calculated by taking the mean time on study in months/years respectively and multiplying by the number of subjects in the Safety Population.

## 8.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Age at screening, gender, race and ethnicity will be summarised for the Safety Population.

Time since diagnosis (years) will be calculated as:

((Date of Informed Consent) – (Date of Diagnosis))/365

Should the day of diagnosis be missing then it will be taken as 01. Should the month of diagnosis be missing it will be taken as January.

Time since diagnosis, lowest basal FVIII level, gene defect (intron 1 inversion, intron 22 inversion, other) and family history of Haemophilia A will be summarised for the Safety Population.

Mutations from previous genotyping and details of family members with a history of Haemophilia A will be listed only.

## 8.3. MEDICAL HISTORY

Medical history will be coded using MedDRA Version 16.1.

Medical history will be listed. The listing will indicate whether or not an event is ongoing, as noted in the CRF.

Medical history will be summarised using the Safety Population. Summaries will be provided for past events, ongoing events and all events (past and ongoing). In the summary tables, system organ classes will be ordered alphabetically. Preferred terms within system organ class will also be order alphabetically.

## 8.4. PRIOR AND CONCOMITANT MEDICATIONS

Prior and concomitant medications will be coded to the preferred name using WHO Drug version 1 March 2013. Note, prior medications do not include FVIII containing products and/or blood products taken prior to entering the study. These are listed separately.

Prior medications are defined as those medications started prior to the date of the first infusion of Optivate®. Concomitant medications are those taken on or after the date of the first infusion of Optivate®. Note, a medication started prior to but continuing after the first infusion of Optivate® will be classed as both prior and concomitant.

Should the start day of the medication be missing, for the purposes of assigning prior/concomitant status, the day will be taken to be 01, unless the month and year are the same as the month and year of first infusion of Optivate®, in which case the date of first infusion of Optivate® will be taken.

Should the start day and month be missing, for the purposes of assigning prior/concomitant status, the day and month will be taken to be 01 January, unless the year is the same as the year of first infusion of Optivate®, in which case the date of first infusion of Optivate® will be taken.

All medications will be listed in order of start date. The listing will identify prior medications.

Prior and concomitant medications will be summarised separately for the Safety Population. Summaries will show the number and percent of subjects taking medications coded to the given preferred term. Summary tables will be sorted alphabetically by preferred name.

# 9. EFFICACY

## 9.1. PRIMARY EFFICACY ENDPOINT AND ANALYSIS

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

Pre-bolus blood samples for quantitative assays will be collected at the Screening Visit, Baseline Visit (Visit 1), Visit 2, Visit 3, the End of Study Visit (Visit 4) and possibly also at unscheduled visits if deemed necessary.

Inhibitor screen data will be listed only.

Quantitative inhibitor results will be listed.

Summaries of quantitative inhibitor levels will be based on both the Per Protocol and Safety populations.

At each visit, the number and percentage of subjects with positive (≥ 0.6 Bethesda Units) and negative (< 0.6 Bethesda Units) results will be summarised.

Shift tables cross tabulating positive/negative status (based on the Bethesda assay) at the Baseline Visit against those at Visits 2, 3 and 4 will be presented. Shifts from the Baseline Visit to any unscheduled visits will also be summarized. Note, should a subject have more than one unscheduled visit then the worst case assessment (positive) will be used in the summary.

The number of exposure days until development of inhibitors (positive status) will be summarized.

## 9.2. SECONDARY EFFICACY ENDPOINTS AND ANALYSES

### 9.2.1. Recovery with current FVIII (Screening Visit) versus 1st dose with Optivate® (Visit 1)

All recoveries will be calculated from incremental FVIII values (i.e. actual values minus pre-infusion values) using the vial label content as provided by BPL. 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 70 minutes post-infusion, samples taken after this time point will be discussed with the Sponsor and a decision whether to exclude the result will be made. Calculations will be based on the peak values obtained at actual post-infusion times, rather than those scheduled in the protocol.

FVIII levels will be reported in IU/dL and will be converted to IU/dL for the listings and calculation of incremental recovery.

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

Recovery with current FVIII and first dose with Optivate® will be summarised.

Results will be tested for the normality of distribution using the Shapiro-Wilk test and if there is no strong evidence against normality, an Analysis of Variance (ANOVA) will be performed for the above recovery comparison.

The ANOVA model will include factors for subject and FVIII product (current FVIII versus Optivate®). Adjusted means for each product will be presented, in addition to the estimate and 95% confidence interval for the difference between products. The p-value for the hypothesis of equal recovery between the products will also be presented.

The analysis will be performed on both the Per Protocol and the Safety populations.

### 9.2.2. Recovery at 1 ED (Visit 1), 10-15 EDs (Visit 2), 50-75 EDs (Visit 3) and 100 EDs (Visit 4)

For Visit 1 (1 ED), Visit 2 (10-15 ED), Visit 3 (50-75 ED) and Visit 4 (100 ED), recovery will be calculated using the formula in 9.2.1.

Recovery will be summarised by visit, batch and subject.

An ANOVA will be performed to compare recovery values at Visit 1, Visit 2, Visit 3 and Visit 4. The model will include factors for subject and visit. Adjusted means for each visit will be presented, in addition to the estimates and 95% confidence intervals for the differences between visits. The p-value for the hypothesis of equal recovery between visits will also be presented.

An ANOVA will be performed to compare recovery values for each batch. The model will include factors for subject, visit and batch. Adjusted means for each batch will be presented, in addition to the estimates and 95% confidence intervals for the differences between batches. The p-value for the hypothesis of equal recovery between batches will also be presented.

The primary analysis will be performed using the Per Protocol Population. A secondary analysis will be conducted on the Safety Population. The summary by subject will be for the Safety population only.

### 9.2.3. Optivate® Therapy to Treat Break Through Bleeds

The following will be summarised using both the Per Protocol Population and Safety Population:

- The number and percentage of subjects with break-through bleeds and the number of break-through bleeds in total.
- The number of break-through bleeds per subject.
- The number and percentage of subjects with minor, major and emergency bleeds and the number of minor, major and emergency bleeds in total. This summary will be repeated but using assessments assigned by the investigator where this disagrees with the subject assessment. Should a bleed change severity, the worst case severity will be used in the summaries.
- The duration of bleeds (minutes), calculated for each individual bleed as:
  the stop time (in minutes) minus the start time (in minutes) + 1.
  Note, this summary will be based on the total number of bleeds.
- The number and percentage of subjects with bleeds located in the joint, muscle, open and other locations.
- The number and percentage of bleeds located in the joint, muscle, open and other locations.
- The number and percentage of subjects with spontaneous bleeds, bleeds due to injury and bleeds due to other causes.
- The number and percentage of spontaneous bleeds, bleeds due to injury and bleeds due to other causes.
- The total number of bleeds per subject will be summarized on a per year and on a per month basis.

The investigator's and subject's assessments of effectiveness of Optivate® to treat bleeds will be summarised separately. The tables will summarise the number and percentage of subjects with responses in each category, the best response for each subject, and the number and percentage of bleeds in each category. Summaries will be based on both the Per Protocol Population and Safety Population.

### 9.2.4. Optivate® Exposure Days

An exposure day is defined as a day in which the subject has received at least one dose of Optivate®. The number of exposure days will be listed for each subject. Descriptive statistics will be presented for the number of exposure days per subject.

For each subject the number of exposure days per month and the number of exposure days per year will be calculated as follows:

$$\text{Number of exposure days per year} = \frac{\text{Number of exposure days captured during the study}}{\text{Time on study}} \times 365$$

$$\text{Number of exposure days per month} = \frac{\text{Number of exposure days captured during the study}}{\text{Time on study}} \times 28$$

where time on study = Date of Visit 4 (end of study visit)/withdrawal visit – Date of Baseline visit + 1

These will also be summarised.

Summaries of exposure days will be based on both the Per Protocol Population and Safety Population. NB: In the case of treatment for surgery, if anti-fibrinolytic agents have been administered (pre or post surgery) then these exposure days will be excluded from the Optivate® exposure day calculation.

### 9.2.5. Optivate® Consumption

Total dose in IU/kg of Optivate® and average dose per infusion per subject will be summarised overall and by the following categories:

- Prophylactic use
- To treat a bleed
- Additional preventative use
- Other reason

The total number of infusions of Optivate® per subject will be summarized overall and by the above categories.

Total dose and total number of infusions, overall and by the above categories will also be summarized on a per year and on a per month basis. These will be calculated as for the number of exposure days per year/per month, described in Section 9.2.4.

The average dose of Optivate® per infusion across all infusions will also be summarized.

Summaries will be based on both the Per Protocol Population and Safety Population.

### 9.2.6. Genotype Analysis

Data on the mutation type for each subject will be listed only.

# 10. SAFETY

Safety data will be summarised using the Safety Population. No formal hypothesis testing will be carried out.

The following will be used to assess the safety of Optivate®:

- Adverse events
- Viral serology
- Physical/medical examination
- Inhibitor development (although this is a safety measurement and will be assessed as the primary efficacy endpoint)

## 10.1. TREATMENT COMPLIANCE

Treatment compliance will not be assessed.

## 10.2. ADVERSE EVENTS

Adverse events will be coded to system organ classes and preferred terms using MedDRA version 16.1.

Treatment emergent AEs are defined as events that have onset following the first infusions of Optivate®, or events present before the first infusion of Optivate®, but which worsen in severity following the first infusion of Optivate®. Should the time of onset be missing, but the date of onset be equal to the date of first dosing with Optivate®, then it will be assumed such events are treatment emergent.

Should the day of onset be missing, for the purposes of assigning treatment emergence, the day will be taken to be 01, unless the month and year are the same as the month and year of first infusion of Optivate®, in which case the date of first infusion of Optivate® will be taken.

Should the day and month be missing, for the purposes of assigning treatment emergence, the day and month will be taken to be 01 January, unless the year is the same as the year of first infusion of Optivate®, in which case the date of first infusion of Optivate® will be taken.

All adverse events will be listed, however only treatment emergent adverse events will be included in the summary tables.

Where severity or causality is missing for an event, for the purposes of the tables, these will be assumed to be severe and very likely/certain respectively. Similarly, where severity or causality changes during the course of the event, the worst case will be taken for the analysis.

Summary tables presenting frequency of AEs by SOC and PT will be ordered by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT.

The following tables of adverse events will be produced:

- An overall summary of the number and percentage of subjects reporting TEAEs, serious TEAEs, treatment related TEAEs, TEAEs leading to withdrawal and TEAEs leading to death
- TEAEs overall and by system organ class and preferred term
- Study treatment related TEAEs overall and by system organ class and preferred term. Study-treatment related events are those recorded as having a possible, probable, or very likely/certain causality related to Optivate®.
- TEAEs by maximum severity, overall and by system organ class and preferred term
- Serious TEAEs, overall and by system organ class and preferred term
- Study treatment related serious TEAEs overall and by system organ class and preferred term. Study-treatment related events are those recorded as having a possible, probable, or very likely/certain causality related to Optivate®.
- TEAEs by maximum relationship to study treatment, overall and by system organ class and preferred term
- TEAEs leading to drug withdrawal, overall and by system organ class and preferred term

Where a subject has multiple events within a given system organ class or preferred term, the subject will only be counted once within that system organ class or preferred term.

For summaries by severity or relationship to study treatment, where a subject has multiple events within a given system organ class or preferred term, the subject will

only be counted once at the maximum severity/worst case relationship at which an event occurred within that system organ class or preferred term.

## 10.3. VIRAL SEROLOGY

Viral serology will be assessed by the central safety laboratory. Serum samples for all viral serology testing will be collected pre-dose at the Baseline Visit (Visit 1) and at the End of Study Visit (Visit 4).

All viral serology data will be listed.

Summary tables will present the number of subjects with positive and negative serology results at each visit. A shift table will also be presented cross tabulating the results at Baseline Visit and End of Study.

## 10.4. PHYSICAL/MEDICAL EXAMINATION

A physical examination is performed at Screening and at Visit 4. At Screening any abnormal findings are recorded on the medical history page. At Visit 4 any abnormal findings are recorded as adverse events.

Data as to whether or not the physical examination was performed and whether there were any changes at Visit 4 from Screening will be listed only. Actual physical examination abnormalities will be summarised and listed with the medical history (Screening physical examination) and adverse event (Visit 4 physical examination) data.

Height and weight data will be listed only.

# 11. INTERIM ANALYSES

There is no planned interim analysis.

# 12. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

There are no changes to the analyses planned in the protocol.

# 13. REFERENCE LIST

1. Committee for Medicinal Products for Human Use (CPMP) Guideline on the Clinical Investigation of Recombinant and Human Plasma-Derived Factor VIII Products (21 July 2011) EMA/CHMP/BPWP/144533/2009.

2. Summary of Product Characteristics for Optivate®.

# 14. PROGRAMMING CONSIDERATIONS

All tables, data listings, figures (TLFs), and statistical analyses will be generated using SAS® for Windows, Release 9.3 (SAS® Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

## 14.1. GENERAL CONSIDERATIONS

- A separate SAS® program will be created for each output.
- Each output will be stored in a separate file.
- Output files will be delivered in Word format.
- Numbering of TFLs will follow ICH E3 guidance.

## 14.2. TABLE, LISTING, AND FIGURE FORMAT

### 14.2.1. General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8
- The data displays for all TLFs will have a 1.5-inch binding margin on top of a landscape oriented page and a minimum 1-inch margin on the other 3 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified
- Specialised text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., $cm^2$, $C_{max}$) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

### 14.2.2. Headers

- All output should have the following header at the top left of each page:
  Bio Products Laboratory Limited
  Protocol 8VWF07
  Study Medication: Optivate®
- All output should have Page n of N at the top or bottom right corner of each page. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date (date output was generated) should appear along with program name and location as the last footer on each page.

### 14.2.3. Display Titles

- Each TLF should be identified by the designation and a numeral. (i.e., Table 14.1.1). A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents. The title is centered. The analysis population should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
ITT Population

### 14.2.4. Column Headers

- Column headings should be displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, include “unit” in column or row heading when appropriate.
- Population sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the ‘n’ used for

the descriptive statistics representing the number of subjects in the population with the respective data.

- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable).

### 14.2.5. Body of the Data Display

#### 14.2.5.1. General Conventions

Data in columns of a table or listing should be formatted as follows:

- alphanumeric values are left-justified;
- whole numbers (e.g., counts) are right-justified; and
- numbers containing fractional portions are decimal aligned.

#### 14.2.5.2. Table Conventions

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

| Severity Rating | N |
|---|---|
| severe | 0 |
| moderate | 8 |
| mild | 3 |

Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).

- Unless otherwise specified in the mock table, where the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups should be included.
- Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the original values, and standard deviations should be printed out to 2 more significant digits than the

original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

| | |
|---|---|
| N | XX |
| Mean | XXX.X |
| Std Dev | X.XX |
| Median | XXX.X |
| Minimum | XXX |
| Maximum | XXX |

- P-values should be output in the format: "0.xxx", where xxx is the value rounded to 3 decimal places. Any p-value less than 0.001 will be presented as <0.001. If the p-value should be less than 0.0001 then present as <0.0001. If the p-value is returned as >0.999 then present as >0.999
- Percentage values should be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Unless otherwise noted, for all percentages, the number of subjects in the analysis population for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% should be presented as 100%, without any decimal places.
- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis population presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed.
- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject should be included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.
- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

### 14.2.5.3. Listing Conventions

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time.
- Dates should be printed in SAS® DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates should be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "NA", unless otherwise specified.

- All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available

#### 14.2.5.4. Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

### 14.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with “Note:” if an informational footnote, or a, b, c, etc. if a reference footnote. Each new footnote should start on a new line where possible.
- Footnotes will be present on the page where they are first referenced and thereafter on each page of the table, unless the footnote is specific only to certain pages. Subject specific footnotes should be avoided.
- Footnotes will be used sparingly and must add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., ‘Program : myprogram.sas Listing source: 16.x.y.z’).

# 15. QUALITY CONTROL

SAS® programs are developed to produce clinical trial output such as analysis data sets, summary tables, data listings, figures or statistical analyses. INC Research SOP 03.010.00 and 03.013.00 provide an overview of the development of such SAS® programs.

INC Research SOP 03.009.00 describes the quality control procedures that are performed for all SAS® programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS® programs produce the proper clinical trial output by checking for their logic, efficiency and commenting and by review of the produced output.

Double programming, lead statistician review and senior statistical review will be implemented for all analysis data sets, summary tables, data listings, figures and statistical analyses. Deviations from this will be highlighted in a quality control tracker spreadsheet. For example it may be more appropriate for a given figure to be validated against an existing summary table as opposed to double programming.

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# 19. MOCK-UPS

## 19.1. TABLE MOCK-UPS

Table mock-ups are provided as an attachment to the SAP.

## 19.2. FIGURE MOCK-UPS

Not applicable.

## 19.3. LISTING MOCK-UPS

Listing mock-ups are provided as an attachment to the SAP.