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

Summary

EudraCT number	2012-004606-10
Trial protocol	DE GB PL
Global end of trial date	31 August 2017

Results information

Result version number	v1 (current)
This version publication date	23 March 2018
First version publication date	23 March 2018

Trial information

Trial identification

Sponsor protocol code	8VWF07

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01811875
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bio Products Laboratory Limited
Sponsor organisation address	Dagger Lane, Elstree, United Kingdom, WD6 3BX
Public contact	Medical Department, Bio Products Laboratory Limited (BPL), +44 (0)2089572297, lisa.wilson@bpl.co.uk
Scientific contact	Medical Department, Bio Products Laboratory Limited (BPL), +44 (0)2089572297, lisa.wilson@bpl.co.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2017
Global end of trial reached?	Yes
Global end of trial date	31 August 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

For each of the five recovery assessments the patients had to give blood samples a number of times over the course of 1 hour. Collection of blood samples may lead to bruising or tenderness at the site where blood is collected. Therefore, to minimise distress the subjects were offered a cannula which could be used to take repeated blood samples.

Background therapy:

There were no comparator tests or products used in this trial.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	01 July 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Colombia: 4
Worldwide total number of subjects	7
EEA total number of subjects	3

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	1

Adults (18-64 years)	6
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First patient first visit: 21-Nov-2014
Last patient first visit: 02-Mar-2017
Last patient last visit: 31-Aug-2017

4 patients recruited in Colombia
2 patients recruited in Poland
1 patient recruited in Germany

Pre-assignment

Screening details:

Screening took place within 4 weeks before the Baseline Visit (V1). A three day wash-out period was required. A brief physical and medical examination was performed and the medical history recorded. Blood samples were taken for viral serology; CD4 count; to measure inhibitor status and FVIII recovery.

Period 1

Period 1 title	Screening period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Arm title	Screening

Arm description:

Following a 3 day washout period, eligible subjects provided a blood sample to test for FVIII inhibitors (pre-bolus only).
Subjects also underwent a recovery assessment at this visit using the subject's current FVIII concentrate (30 IU/kg dose).
Blood samples were 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)

Arm type	Experimental
Investigational medicinal product name	Current FVIII Product
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

Subjects underwent a recovery assessment at this visit using the subject's current FVIII concentrate (30 IU/kg dose).

Number of subjects in period 1	Screening
Started	7
Completed	7

Period 2	
Period 2 title	Baseline(V1)/ Treatment period (V1-V4)
Is this the baseline period?	Yes[1]
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Arm title	Optivate 500IU

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Optivate 500IU
Investigational medicinal product code	B02BD02
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

- Bolus dose study visits 1-4: 30 IU/kg

- Routine prophylaxis: 20-40 IU/kg to be administered 3 times a week for at least 100 exposure days.

- Preventative therapy: single dose of 20-40 IU/kg to be administered.

- Minor bleeds: 8-15 IU/kg (Repeated every 12 to 24 hours. At least 1 day, until the bleeding episode as indicated by pain is resolved or healing was achieved)

- More extensive haemarthrosis, muscle bleeding or haematoma: 12-23 IU/kg (Repeat infusion every 12 to 24 hours for 3 to 4 days or more until pain and acute disability are resolved).

- Life-threatening haemorrhages: 23-37IU/kg (Repeat infusion every 8 to 24 hours until threat resolved).

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 is the screening period. Subjects must complete the screening period before entering Period 2(baseline period).

Number of subjects in period 2	Optivate 500IU
Started	7
Completed	6
Not completed	1
Adverse event, serious fatal	1

Period 3

Period 3 title	Follow-up period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Arm title	Follow-up period

Arm description:

Follow-up period was conducted by telephone call 28 days after the last Optivate® infusion to allow follow-up of any AEs.

Arm type	Experimental
Investigational medicinal product name	Optivate 500IU
Investigational medicinal product code	B02BD02
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

- Bolus dose study visits 1-4: 30 IU/kg

- Routine prophylaxis: 20-40 IU/kg to be administered 3 times a week for at least 100 exposure days.

- Preventative therapy: single dose of 20-40 IU/kg to be administered.

- Minor bleeds: 8-15 IU/kg (Repeated every 12 to 24 hours. At least 1 day, until the bleeding episode as indicated by pain is resolved or healing was achieved)

- More extensive haemarthrosis, muscle bleeding or haematoma: 12-23 IU/kg (Repeat infusion every 12 to 24 hours for 3 to 4 days or more until pain and acute disability are resolved).

- Life-threatening haemorrhages: 23-37IU/kg (Repeat infusion every 8 to 24 hours until threat resolved).

Number of subjects in period 3	Follow-up period
Started	6
Completed	6

Baseline characteristics

Reporting groups

Reporting group title	Baseline(V1)/ Treatment period (V1-V4)

Reporting group description: -

Reporting group values	Baseline(V1)/ Treatment period (V1-V4)	Total	
Number of subjects	7	7	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	1	1	
Adults (18-64 years)	6	6	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	0	0	
Male	7	7	
Race Units: Subjects			
Caucasian/White	2	2	
Other	5	5	
Ethnicity Units: Subjects			
Hispanic or Latino	5	5	
Not Hispanic or Latino	2	2	

End points

End points reporting groups

Reporting group title	Screening
Reporting group description:	
Following a 3 day washout period, eligible subjects provided a blood sample to test for FVIII inhibitors (pre-bolus only). Subjects also underwent a recovery assessment at this visit using the subject's current FVIII concentrate (30 IU/kg dose). Blood samples were 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)	
Reporting group title	Optivate 500IU
Reporting group description: -	
Reporting group title	Follow-up period
Reporting group description:	
Follow-up period was conducted by telephone call 28 days after the last Optivate® infusion to allow follow-up of any AEs.	
Subject analysis set title	Protocol population
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects who completed at least 100 exposure days with Optivate.	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects who took at least part of one dose of Optivate	

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

End point title	To assess post-marketing immunogenicity of Optivate by monitoring plasma inhibitor levels for at least 100 Exposure Days for each subject.
End point description:	
FVIII inhibitor status at any of the study visits was measured by a Nijmegen Bethesda assay and inhibitor screens. A result of ≥ 0.6 BU confirmed that the subject had developed inhibitors to FVIII. If this occurred, the test was repeated on a separate sample; if both tests were confirmed to be ≥ 0.6 BU, this was to be reported by the Investigator as a serious adverse event (SAE).	
End point type	Primary
End point timeframe:	
Over a period of 12 months	

End point values	Optivate 500IU	Protocol population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	5	5		
Units: <0.6 BU				
number (not applicable)	5	5		

Statistical analyses

Statistical analysis title	Primary efficacy endpoint

Statistical analysis description:

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

Comparison groups	Optivate 500IU v Protocol population
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Quantitative inhibitor levels of ≥0.6BU
Point estimate	0
Confidence interval	
level	Other: 0 %
sides	1-sided
upper limit	0

Notes:

[1] - Shift tables cross-tabulating positive/negative status (based on the Nijmegen-Bethesda assay) at the Baseline Visit (Visit 1) against those at Visits 2, 3, and 4 were analysed.

Secondary: To assess efficacy of Optivate by monitoring prior FVIII recovery (Screening Visit) versus first dose with Optivate® (Visit 1).

End point title	To assess efficacy of Optivate by monitoring prior FVIII recovery (Screening Visit) versus first dose with Optivate® (Visit 1).

End point description:

Recovery with prior FVIII concentrate (Screening Visit) versus first dose with Optivate® (Visit 1).

End point type	Secondary

End point timeframe:

Over a period of 12 months

End point values	Optivate 500IU	Protocol population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	5	5		
Units: IU/dL per IU/kg				
arithmetic mean (confidence interval 95%)	-0.91 (-1.87 to 0.04)	-0.91 (-1.87 to 0.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Optivate® Recovery Over Time (Recovery at 1 Exposure Day [ED, Visit 1], 10 to15 EDs [Visit 2], 50 to 75 EDs, [Visit 3], and 100 EDs [Visit 4]) for the Protocol Population.

End point title	Optivate® Recovery Over Time (Recovery at 1 Exposure Day [ED, Visit 1], 10 to15 EDs [Visit 2], 50 to 75 EDs, [Visit 3], and 100 EDs [Visit 4]) for the Protocol Population.

End point description:

A recovery assessment was conducted at each study visit. Recovery assessments were only conducted after a 3-day washout period and when the subject was not actively bleeding.
At the Screening Visit, subjects who had completed a 3-day washout period and were not actively bleeding were dosed with 30 IU/kg of their prior FVIII concentrate. The dose was measured to the nearest 0.1 mL. Blood samples for the recovery assessment were to be collected at the following time points:
• Predose
• 15 minutes postinfusion (±5 minutes).
• 30 minutes postinfusion (±5 minutes).
• 1 hour postinfusion (±10 minutes).
Actual times of sample collection were to be recorded in the CRF

At visits 1, 2, 3 and 4 subjects were dosed with 30 IU/kg of Optivate and blood samples for recovery assessments were taken at the same timepoints as specified above.

End point type	Secondary

End point timeframe:

Over a period of 12 months

End point values	Optivate 500IU	Protocol population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	5	5		
Units: IU/dL per IU/kg				
arithmetic mean (confidence interval 95%)	-0.01 (-1.72 to 1.70)	-0.01 (-1.72 to 1.70)		

Statistical analyses

No statistical analyses for this end point

Secondary: Optivate® therapy to treat breakthrough bleeds per subject per year in the protocol population.

End point title	Optivate® therapy to treat breakthrough bleeds per subject per year in the protocol population.

End point description:

Number of breakthrough bleeds per subject per year in the protocol population.

End point type	Secondary

End point timeframe:

Over a period of 12 months

End point values	Optivate 500IU	Protocol population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	5	5		
Units: Bleeds per subject per year				
arithmetic mean (standard deviation)	3.99 (± 2.961)	3.99 (± 2.961)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall consumption of Optivate®: Number of exposure days for each subject per year/subject in the per protocol population.

End point title	Overall consumption of Optivate®: Number of exposure days for each subject per year/subject in the per protocol population.

End point description:

Number of exposure days for each subject per year/subject in the per protocol population.

End point type	Secondary

End point timeframe:

Over a period of 12 months

End point values	Optivate 500IU	Protocol population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	5	5		
Units: Days				
arithmetic mean (standard deviation)	116.2 (± 18.12)	116.2 (± 18.12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall consumption of Optivate®: Total dose in IU/kg of Optivate® per subject for prophylactic use.

End point title	Overall consumption of Optivate®: Total dose in IU/kg of Optivate® per subject for prophylactic use.

End point description:

Total dose in IU/kg of Optivate® per subject for prophylactic use

End point type	Secondary

End point timeframe:

Over a period of 12 months

End point values	Optivate 500IU	Protocol population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	5	5		
Units: IU/kg				
arithmetic mean (standard deviation)	3639.97 (± 993.464)	3639.97 (± 993.464)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall consumption of Optivate®: Total dose in IU/kg of Optivate® per subject to treat a bleed in the protocol population.

End point title	Overall consumption of Optivate®: Total dose in IU/kg of Optivate® per subject to treat a bleed in the protocol population.

End point description:

Total dose in IU/kg of Optivate® per subject to treat a bleed in the protocol population.

End point type	Secondary

End point timeframe:

Over a period of 12 months

End point values	Optivate 500IU	Protocol population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	5	5		
Units: IU/kg				
arithmetic mean (standard deviation)	97.72 (± 117.086)	97.72 (± 117.086)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall consumption of Optivate®: Total number of infusions for prophylactic use per subject in the protocol population.

End point title	Overall consumption of Optivate®: Total number of infusions for prophylactic use per subject in the protocol population.

End point description:

Total number of infusions for prophylactic use per subject in the protocol population.

End point type	Secondary

End point timeframe:

Over a period of 12 months

End point values	Optivate 500IU	Protocol population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	5	5		
Units: Infusions				
arithmetic mean (standard deviation)	116.8 (± 17.66)	116.8 (± 17.66)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall consumption of Optivate®: Total number of infusions to treat a bleed per subject in the protocol population.

End point title	Overall consumption of Optivate®: Total number of infusions to treat a bleed per subject in the protocol population.

End point description:

Total number of infusions to treat a bleed per subject in the protocol population.

End point type	Secondary

End point timeframe:

Over a period of 12 months

End point values	Optivate 500IU	Protocol population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	5	5		
Units: Infusions				
arithmetic mean (standard deviation)	2.4 (± 3.21)	2.4 (± 3.21)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall consumption of Optivate®: Overall mean dose in IU/kg of Optivate® per subject/year for prophylactic use in the protocol population.

End point title	Overall consumption of Optivate®: Overall mean dose in IU/kg of Optivate® per subject/year for prophylactic use in the protocol population.

End point description:

Overall mean dose in IU/kg of Optivate® per subject/year for prophylactic use in the protocol population.

End point type	Secondary

End point timeframe:

Over a period of 12 months

End point values	Optivate 500IU	Protocol population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	5	5		
Units: IU/kg				
arithmetic mean (standard deviation)	3890.02 (± 1033.993)	3890.02 (± 1033.993)		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment emergent adverse events (non-serious) in the safety population

End point title	Treatment emergent adverse events (non-serious) in the safety population

End point description:

End point type	Secondary

End point timeframe:

Over a period of 12 months

End point values	Optivate 500IU	Safety population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	7	7		
Units: treatment emergent events				
number (not applicable)	6	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment emergent adverse events (serious) in safety population

End point title	Treatment emergent adverse events (serious) in safety population

End point description:

Treatment emergent adverse events (serious) in safety population

End point type	Secondary

End point timeframe:

Over a period of 12 months

End point values	Optivate 500IU	Safety population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	7	7		
Units: treatment emergent events				
number (not applicable)	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Inhibitor Development: Positive FVIII inhibitor status in safety population (measured by ≥0.6 Bethesda units)

End point title	Inhibitor Development: Positive FVIII inhibitor status in safety population (measured by ≥0.6 Bethesda units)

End point description:

Inhibitor Development: Positive FVIII inhibitor status in safety population measured by ≥0.6 Bethesda units (this was a safety measurement but was assessed as a primary efficacy endpoint).

End point type	Secondary

End point timeframe:

Over a period of 12 months

End point values	Optivate 500IU	Safety population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	7	7		
Units: ≥0.6 Bethesda units				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Over a period of 12 months

Adverse event reporting additional description:

Patients had an electronic diary where they could enter any adverse events they experienced in between study visits. Adverse events were assessed at each study visit otherwise.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	Safety Population

Reporting group description:

Safety population includes all subjects who took at least part of one dose of Optivate.

Serious adverse events	Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 7 (28.57%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Injury, poisoning and procedural complications			
Fatal road traffic accident			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			
Asthmatic crisis			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Safety Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 7 (57.14%)		
Injury, poisoning and procedural complications			
ANKLE TRAUMA			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
SOFT TISSUE TRAUMA LEFT HAND			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
ANEMIA			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
General disorders and administration site conditions			
GENERAL PAIN			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
BRONCHOSPASM			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
HEMARTHROSIS OF RIGHT ELBOW			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
JOINT PAIN			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
HEMARTHROSIS OF RIGHT KNEE			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Infections and infestations			
COMMON COLD			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 December 2014	Update to responsible medical officer.
23 March 2015	Update to Responsible Medical Officer.
30 November 2015	- Protocol to clarify that the end of trial will be when the 10th patient has completed their follow-up visit. - Third exclusion criterion updated to clarify and to be consistent with routine clinical practice and the patient information sheet that subjects will be excluded if they have symptomatic liver or renal disease. In addition, section updated to state that historical lab results for ALT and creatinine (within the last 12 months) would be acceptable instead of a new sample being taken at screening. If historical results are not available, then an ALT and creatinine sample is not required at screening as long as the patient is asymptomatic. - Product Presentation updated to state that a field for batch specific potency was not included on the approved product label in error. Protocol updated to provide clarification on where actual vial content can be established from i.e. certificate of analysis. - Dosage to treat breakthrough bleeds updated to clarify what dose may be taken in the event that a bleed occurs on the same day as the routine prophylactic dose. - Screening Procedures Before Dosing updated to state that all bleeds regardless of severity, from the past 12 months should be recorded in the eCRF.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported