25 June 2015
EMA/CHMP/492782/2015
Committee for Medicinal Products for Human Use (CHMP)

CHMP group of variations including an extension of indication assessment report

Invented name: Voncento

International non-proprietary name (INN)/Common name: Human coagulation Factor VIII/ human von WILLEBRAND Factor

Procedure No. EMEA/H/C/002493/II/0008/G

Marketing authorisation holder (MAH): CSL Behring GmbH

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List of abbreviations

AHF	Anti-haemophilic factor
ALT	Alanine transaminase
ANOVA	Analysis of variance
AST	Aspartate transaminase
ATC	Acute toxic class
AUC	Area under the curve
BU	Bethesda Units
BW	Body Weight
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
Cl	Total of the study drug from the body
Cmax	Maximum plasma concentration
Cmin	Minimum plasma concentration
CRF	Case report form
CV%	Coefficient of variation as percentage
DDAVP	1-deamino-8-D-arginine vasopressin, desmopressin acetate
FVIII:C	Factor VIII:Coagulant
HIV	Human immunodeficiency virus
HMW	High molecular weight
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
ITI	Immune Tolerance Induction
IU	International Unit(s)
i.v.	Intravenous(ly)
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantification
LMW	Low Molecular Weight
MCV	Mean corpuscular volume
MedRA	Medical Dictionary for Regulatory Activities
MRT	Mean residence time
NOAEL	No Observed Adverse Effect Level
NSAID	Non-steroidal anti-inflammatory drug
NSB	Non Surgical Bleed
P80	Polysorbaat 80
PIP	Pediatric Investigation Plan
PMS	Postmarketing Surveillance Study
PP	Per-protocol
PTP	Previously treated patient
RBC	Red blood cell
SAP	Statistical Analysis Plan
SPF	Specific Pathogen Free
TEAE	Treatment-emergent adverse event
TGA	Therapeutic Goods Administration
Tmax	Time the maximum concentration occurs
TNBP	Tri-n-butyl Phosphate
ULN	Upper limit of normal
Vss	Volume of distribution at steady state
VWD	Von Willebrand disease
VWF	Von Willebrand Factor
VWF:Ag	Von Willebrand Factor:Antigen
VWF:CB	Von Willebrand Factor:Collagen Binding
VWF:Rco	Von Willebrand Factor:Ristocetin Co-factor
WBC	White blood cell
WP	Weibal Pallade Bodies

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, CSL Behring GmbH submitted to the European Medicines Agency on 4 September 2014 an application for a group of variations.

This application concerns the following medicinal product:

Centrally authorised Medicinal product(s): **For presentations: See Annex A**	**International non-proprietary name:**
Voncento	HUMAN COAGULATION FACTOR VIII / HUMAN VON WILLEBRAND FACTOR

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIB
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II, IIIA, IIIB

Extension of indication for Voncento to include prophylactic treatment of patients with Von Willebrand Disease (VWD); in addition, the product information has been updated to provide data on the treatment of paediatric patients with VWD. As a consequence, sections 4.1, 4.2, 4.4, 4.9, 5.1 and 5.2 of the SmPC have been updated. The package leaflet was updated accordingly.

Moreover, the MAH took the opportunity to correct the manufacturing sites addresses in Annex II and to make editorial changes to the product information.

The group of variations proposed amendments to the Summary of Product Characteristics, Labelling, Package Leaflet and Annex II.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0123/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0123/2014 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No

847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Pieter de Graeff Co-Rapporteur: Greg Markey

Timetable	Dates
Submission date	4 September 2014
Start of procedure:	19 September 2014
CHMP Rapporteur Assessment Report	20 November 2014
CHMP (Co)-Rapporteur AR	19 November 2014
PRAC Rapporteur Assessment Report	18 November 2014
PRAC Rapporteur Updated Assessment Report	26 November 2014
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	4 December 2014
Request for supplementary information (RSI)	18 December 2014
MAH's responses submitted to the CHMP on:	18 March 2015
CHMP (Co)-Rapporteur AR on the MAH's responses circulated on:	23 April 2015
PRAC Rapporteur Assessment Report	28 April 2015
PRAC Rapporteur Updated Assessment Report	n/a
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	7 May 2015
CHMP (Co)-rapporteur's updated assessment report:	17 May 2015
2nd Request for supplementary information (RSI)	21 May 2015
MAH's responses submitted to the CHMP on:	26 May 2015
PRAC Rapporteur Updated Assessment Report	12 June 2015
Joint Rapporteur's updated assessment report circulated on:	12 June 2015
Joint Rapporteur's revised assessment report circulated on:	n/a
CHMP opinion:	25 June 2015

2. Scientific discussion

2.1. Introduction

Von Willebrand Disease (VWD) is a clinically heterogeneous group of disease variants, each characterized by distinct quantitative or qualitative abnormalities in VWF, resulting in defective or deficient function. The prevalence of VWD is reported to be as high as 1-2% in the general population (Mannucci MD, 2004). Patients with VWD are classified into Types 1, 2, and 3.

Type 1: A quantitative defect, in which there are proportional reductions in the levels of the VWF Antigen (VWF:Ag) and VWF function as measured by VWF Ristocetin Cofactor activity VWF:RCo) or Collagen Binding capacity (VWF:CB); reduced level of factor VIII coagulant activity (FVIII:C). Type I VWD is an autosomal dominant disorder and is the most commonly documented form of VWD, accounting for 70-80% of cases.

Type 2 accounts for approximately 20% of all diagnosed cases; *Type 2A:* Qualitatively defective VWF in which the levels of VWF:RCo and VWF:CB are low compared to the levels of VWF:Ag and characterised by absence of HMW multimers; reduced or normal level of FVIII:C. Type 2A VWD is an autosomal dominant disorder. *Type 2B:* Qualitatively defective VWF in which the levels of VWF:RCo and VWF:CB are low compared to the levels of VWF:Ag; increased affinity to platelet glycoprotein Ibα results in loss of HMW multimers and thrombocytopenia; reduced or normal level of FVIII:C. Type 2B VWD is an autosomal dominant disorder. *Type 2M:* Qualitatively defective VWF in which the levels of VWF:RCo and VWF:CB are low compared to the levels of VWF:Ag; no loss of HMW multimers, reduced or normal level of FVIII:C. Type 2M VWD is an autosomal dominant disorder. *Type 2N:* Qualitatively defective VWF in which there is a decreased affinity (abnormal binding) to FVIII; reduced level of FVIII:C. Type 2N VWD is an autosomal dominant disorder.

Type 3: Severe deficiency of VWF characterised by VWF:RCo, VWF:Ag, and FVIII:C levels typically <5% (or virtually immeasurable). Type 3 VWD is an autosomal dominant disorder and it is the rarest form of VWD, it accounts for 1-3% of cases.. Type 3 VWD is very rare and occurs in approximately 1 in 300,000 – 500,000 individuals.

Most patients with Type 1 VWD and sometimes those with Type 2 N VWD may be treated satisfactorily with DDAVP, which releases endogenous VWF from endothelial cells, but for the other types of VWD use of a VWF/FVIII concentrate is necessary in order to achieve haemostasis during bleeds or surgery.

Fibrinolytic inhibitors such as tranexamic acid are frequently also used during bleeds and surgery. Voncento is a human coagulation factor VIII (FVIII)/von Willebrand Factor (VWF) complex and belongs to the pharmacological class of haemostatic agents. This product is administered by intravenous infusion to raise FVIII and VWF levels in patients with corresponding deficiencies. VWF and FVIII are 2 distinct glycoproteins that circulate in plasma in the form of a non-covalently bound complex. Both factors are essential for normal haemostasis in humans. Defects in the VWF/FVIII complex underlie 2 distinct hereditary coagulation disorders: von Willebrand's disease (VWD) and haemophilia A. Marketing authorization was granted in August 2013.

In this variation submission, the MAH applies for an extension of indication for human coagulation FVIII/VWF complex to include prophylactic treatment of patients with VWD as follows:

"Prophylaxis and t~~T~~reatment of haemorrhage or ~~prevention and treatment of~~ surgical bleeding in patients with VWD, when desmopressin (DDAVP) treatment alone is ineffective or contraindicated."

The initial Marketing authorisation application (MAA) in Europe included the interim study report for study CSLCT-BIO-08-54 that presented the results up to the Month 12 visit. In this submission, the interim study

report was replaced by the final study report which included an additional 12 months of prophylaxis treatment results, completing the entire 24-month treatment period of the study.

Furthermore, the MAH proposes to revise the paediatric information in various sections of the SmPC, following the completion of Study CSL-CT-08-52 in children ≤12 years old with VWD. Additionally, an abbreviated study report summarising the results of the discontinued study on immune tolerance induction (ITI) treatment with human coagulation FVIII/VWF complex (study CSLCT-BIO-10-67) was provided to the EMA in June 2014 via an Article 46 submission to update the dossier accordingly.

This application proposes changes in the following main areas of the SmPC.

- The currently approved VWD indication:

"Treatment of haemorrhage or prevention and treatment of surgical bleeding in patients with VWD, when desmopressin (DDAVP) treatment alone is ineffective or contraindicated" is revised as follows:
"Prophylaxis and treatment of haemorrhage or surgical bleeding in patients with VWD, when desmopressin (DDAVP) treatment alone is ineffective or contraindicated."

- Posology section:

As the approved indication so far does not specify age, only a statement in SPC Section 4.2 that *"The safety and efficacy of Voncento in children <12 years have not been established. No data are available."*
The MAH proposes to modify SPC Section 4.2 so that this statement only refers to haemophilia A and to include statements on dosing which would be applicable to paediatric patients from age 1 year and older.

Paediatric development

A Paediatric Investigation plan (PIP) has been approved by the PDCO with modifications (P/0123/2014), in May 2014. In accordance with the PIP, this post-approval variation presents data from clinical studies performed by CSL with human coagulation FVIII/VWF, including new data on the on-demand and prophylaxis treatment in children with VWD.

The following waiver was agreed on the grounds that clinical studies could not be expected to be of significant therapeutic benefit to or fulfil a therapeutic need of the paediatric population:

- In the treatment of hereditary Factor VIII deficiency (Haemophilia A)

The waiver applies to infants from birth to less than 28 days;-
Deferral of completion

Deferral has been agreed on the completion of 3 studies in children under 12 years. Data from two of these studies (CSLCT–BIO-08-52 and the terminated study CSLCT–BIO-10-67) were submitted during this procedure. In accordance with the PIP, paediatric data regarding children aged <12 years with haemophilia A from the ongoing clinical study (CSLCT–BIO-08-53) will be submitted after finalisation of the study.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

No environmental risk assessment (ERA) has been submitted – as per the initial application for the MA for Voncento. The MAH has not performed an Environmental Risk Assessment (ERA) in accordance with the "Guideline on the Environmental Risk Assessment of the medicinal products for human use"

(EMEA/CHMP/SWP/4447/00) – as Voncento is a naturally derived substance and a protein, unlikely to result in significant risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1: Studies providing efficacy data for Von Willebrand disease

Study identifier	Clinical phase Study dates	No. of centres Countries	Study design	Primary objective(s)	Study product(s) Dose regimen	No. of subjects Sex Mean age ±SD (range)	Efficacy variables
Pivotal efficacy and safety studies							
CSLCT-BIO-08-54 (Section 5.3.5.2.2 [VWD])	II/III June 2009 - February 2012	6 Brazil, Bulgaria, Poland, Russia, and Ukraine	Open-label multi-centre study	To investigate the initial and repeat PK profile of Voncento in subjects with VWD. To assess the haemostatic efficacy of Voncento in subjects with VWD who require a VWF product to control an NSB event. To assess the effectiveness of a prophylaxis regime as compared to on-demand therapy with Voncento in preventing NSB events.	Human coagulation FVIII/VWF complex PK component: 80 IU/kg VWF:RCo each for initial and repeat PK. Efficacy component: As required according to the subject's baseline FVIII:C and/or VWF:RCo levels.	22 (Type 1: 5, Type 2A: 4, Type 3: 13) 10 males, 12 females 33.6 ± 15.2 years (15-68 years), including 3 adolescents aged 15-16 years	Haemostatic efficacy, study product usage, blood product transfusion requirements, assessment of blood loss during surgery.

Study identifier	Clinical phase Study dates	No. of centres Countries	Study design	Primary objective(s)	Study product(s) Dose regimen	No. of subjects Sex Mean age ±SD (range)	Efficacy variables
CSLCT-BIO-08-52 (Section 5.3.5.2.6 [VWD])	III July 2010 - August 2013	8 Georgia, Germany, Guatemala, Lebanon, Belarus, Ukraine	Open-label, multi-centre study	To assess the efficacy of Voncento in paediatric subjects with VWD. To investigate the PK profile of Voncento in paediatric subjects with VWD.	Human coagulation FVIII/VWF complex PK component: 80 IU/kg VWF:RCo each for initial and repeat PK. Efficacy component: As required according to the subject's baseline VWF:RCo levels.	17 (Type 2A: 7, Type 3: 10) 7 males, 10 females 5.2 ± 3.4 years (0-11 years), including 9 subjects aged <6 years	Haemostatic efficacy, study product usage, blood product transfusion requirements, assessment of blood loss during surgery.
Supportive efficacy and safety studies							
CSLCT-BIO-03-97 (Section 5.3.5.2.3 [VWD])	II/III December 2004 - May 2007	8 Australia New Zealand	Open-label, multi-centre	To evaluate the efficacy and safety of Voncento in the treatment of NSBs, in the management of surgical procedures and prophylactic therapy in subjects with VWD where DDAVP treatment was ineffective, inadequate, or contraindicated.	Voncento RP As required, dependent on the subject's baseline FVIII:C and/or VWF:RCo levels.	23 (Type 1: 7; Type 2A: 2; Type 2M: 6; Type 3: 7; unknown: 1) 12 males, 11 female 47.2 ± 20.9 years (3-85 years), incl. 1 child aged 3 years	Haemostatic efficacy, plasma levels of FVIII and VWF, blood loss and transfusions, study product usage, number of bleeding events.
Shortt study (Section 5.3.5.2.4 [VWD])	N/A April 2003 - September 2005	3 Australia	Retrospective	To evaluate the safety and efficacy of Voncento use in the prevention of bleeding in VWD subjects undergoing invasive or surgical procedures.	Voncento RP Prophylactic treatment for invasive or surgical procedures.	43 (Type 1: 26; Type 2A: 8; Type 2B: 4; Type 3: 5) 21 male, 22 female 52 years (19-80 years)	Haemostatic efficacy (for surgical events), number of bleeding events.
Howman study (Section 5.3.5.2.5 [VWD])	N/A April 2003 - February 2008	8 Australia New Zealand	Retrospective	To evaluate the efficacy, safety, and dosing of Voncento in the treatment and prevention of bleeding in children and adolescents with VWD.	Voncento RP, SP Treatment for a surgical event, non-surgical bleed or prophylaxis.	43 (Type 1: 21; Type 2A: 4; Type 2B: 6; Type 2M: 4; Type 2N: 1; Type 3: 7) 25 male, 18 female 10 years [a] (5 months – 17.5 years)	Haemostatic efficacy, blood loss, transfusion of other blood products, use of adjunctive therapy, study product usage.

AHF (HP) = Anti-haemophilic factor (High Purity); DDAVP = 1-deamino-8-D-arginine vasopressin, desmopressin acetate; FVIII = human coagulation factor VIII, FVIII:C = FVIII coagulant activity, IU = International Unit; NSB = non-surgical bleeding, PK = pharmacokinetic, RP = reference product, SD = standard deviation, SP = study product, VWD = Von Willebrand disease, VWF = Von Willebrand factor, VWF:RCo = Von Willebrand factor:Ristocetin Cofactor activity. [a] Median

2.3.2. Pharmacokinetics

Special populations

Paediatric population

A paediatric PK, safety, and efficacy study CSLCT-BIO-08-52 in VWD patients was submitted in support of the current application. A total of 17 subjects were enrolled and treated with human coagulation FVIII/VWF complex, 4 with a prophylaxis regimen (Arm 1) and 13 with an on-demand regimen (Arm 2). The mean age of the included patients was 5.2 years (age range 0-11.0 years) with 9 subjects (52.9%) aged <6 years. Seven subjects (41.2%) were male, 10 (58.8%) female. All but 2 subjects were Caucasian. All subjects participated in the initial PK assessment, and 9 subjects with VWD Type 3 participated in the repeat PK assessment. All subjects completed the Month 12 visit.

PK samples were collected immediately prior to dosing and then at 0.5, 4, 8, 24, and 48 h after the infusion. Samples for determination of VWF:RCo, VWF:Ag, VWF:CB, and FVIII:C were taken at each PK time point.

Descriptive statistics for the main PK parameters for baseline-adjusted VWF:RCo, VWF:Ag, and VWF:CB are summarised in table 2. Following infusion with human coagulation FVIII/VWF complex, plasma concentrations of all VWF markers increased immediately, reaching C_{max} at 30 min post-dose, and then declined over time with mean terminal $t_{1/2}$ of 10.3-11.5 h and MRT of 12.7-14.6 h. Profiles of concentrations over time were similar between VWF markers; mean baseline-adjusted plasma concentrations for VWF:RCo were slightly lower than for VWF:Ag and VWF:CB.

Table 2: VWF PK parameters after an initial human coagulation FVIII/VWF complex administration (PK population [N=17]; study CSLCT-BIO-08-52)

PK parameter	VWF:RCo	VWF:Ag	VWF:CB	FVIII:C
IR [(IU/mL)/(IU/kg)]				
N	17	17	17	16
Mean (CV%)	0.014 (19.1)	0.014 (23.7)	0.013 (16.9)	0.019 (45.8)
Median (range)	0.015 (0.009-0.017)	0.014 (0.007-0.022)	0.014 (0.009-0.017)	0.018 (0.008-0.048)
Geometric mean	0.014	0.014	0.013	0.018
$t_{1/2}$ [h]				
N	11	16	16	10
Mean (CV%)	11.3 (49.7)	11.5 (28.3)	10.3 (20.8)	24.0 (52.5)
Median (range)	11.5 (4.13-22.4)	11.3 (7.72-22.4)	10.3 (6.08-15.4)	20.4 (7.05-49.2)
Geometric mean	10.0	11.2	10.0	21.0
C_{max} [IU/mL]				
N	17	17	17	16
Mean (CV%)	1.33 (44.9)	2.07 (48.1)	1.79 (43.5)	0.84 (48.4)
Median (range)	1.23 (0.69-2.76)	1.75 (1.22-5.18)	1.48 (1.13-3.64)	0.74 (0.33-1.67)
Geometric mean	1.23	1.91	1.67	0.75
AUC_{0-t} [h*IU/mL]				
N	17	17	17	16
Mean (CV%)	11.8 (62.4)	25.5 (51.8)	20.2 (50.3)	23.1 (71.3)
Median (range)	10.4 (3.11-29.4)	21.7 (11.7-57.7)	16.5 (11.1-49.0)	19.4 (1.47-59.2)
Geometric mean	9.85	23.0	18.5	16.8
$AUC_{0-\infty}$ [h*IU/mL]				
N	11	16	16	10
Mean (CV%)	15.5 (56.1)	28.4 (51.1)	21.5 (50.5)	35.8 (96.2)
Median (range)	12.9 (4.6-31.7)	23.6 (12.9-61.0)	16.9 (11.7-51.3)	21.1 (1.6-100)
Geometric mean	13.3	25.6	19.6	20.1
CL [mL/h/kg]				
N	11	16	16	10
Mean (CV%)	8.02 (49.2)	5.86 (45.8)	6.73 (27.5)	4.50 (171)
Median (range)	7.22 (2.82-17.3)	4.96 (2.24-13.1)	6.49 (3.66-11.7)	1.63 (0.73-26.1)
Geometric mean	7.23	5.40	6.51	2.26
V_{ss} [mL/kg]				
N	11	16	16	10
Mean (CV%)	90.3 (28.2)	78.3 (27.0)	81.7 (18.5)	70.5 (57.9)
Median (range)	92.4 (52.3-135.3)	70.8 (54.6-133.5)	81.6 (54.7-113.8)	54.4 (33.1-172.9)
Geometric mean	87.0	76.1	80.4	62.8

AUC = area under the concentration curve; CL = clearance; C_{max} = maximum plasma concentration; CV = coefficient of variation; FVIII:C = Factor VIII: coagulant activity; IR = incremental recovery; IU = international units; N = number of evaluable subjects; PK = pharmacokinetics; $t_{1/2}$ = half-life; V_{ss} = volume of distribution at steady state; VWF:Ag = von Willebrand factor: antigen; VWF:CB = von Willebrand factor: collagen binding; VWF:RCo = von Willebrand factor: ristocetin cofactor.

Following repeat treatment with human coagulation FVIII/VWF complex at 6 months, mean plasma concentrations for all VWF markers were comparable to those from the initial PK infusion (Table 3): there was no evidence of alterations which would suggest the development of inhibitors to Voncento.

Table 3: VWF PK parameters after an initial and repeat human coagulation FVIII/VWF complex administration (repeat PK population [N=9 Type 3 VWD subjects], study CSLCT-BIO-08-52)

PK parameter	VWF:RCo	VWF:Ag	VWF:CB	FVIII:C
IR [(IU/mL)/(IU/kg)]				
N	9	9	9	9
Mean (CV%)	0.016 (18.9)	0.013 (16.1)	0.013 (14.3)	0.021 (20.3)
Median (range)	0.017 (0.010-0.020)	0.013 (0.010-0.017)	0.013 (0.011-0.016)	0.021 (0.013-0.028)
Geometric mean	0.016	0.013	0.013	0.020
$t_{1/2}$ [h]				
N	9	9	9	3
Mean (CV%)	13.2 (36.3)	12.6 (20.7)	11.1 (19.3)	34.7 (25.5)
Median (range)	14.5 (3.71-17.8)	11.9 (9.61-18.4)	10.9 (8.46-14.8)	37.1 (24.9-42.1)
Geometric mean	12.1	12.4	11.0	33.9
C_{max} [IU/mL]				
N	9	9	9	9
Mean (CV%)	1.44 (18.2)	2.01 (27.6)	1.78 (19.8)	0.90 (36.5)
Median (range)	1.41 (1.07-1.99)	1.95 (1.31-3.10)	1.62 (1.41-2.54)	0.79 (0.39-1.55)
Geometric mean	1.42	1.94	1.75	0.85
AUC_{0-t} [h*IU/mL]				
N	9	9	9	9
Mean (CV%)	14.3 (36.8)	28.3 (34.3)	23.6 (33.7)	31.2 (45.9)
Median (range)	14.3 (6.82-24.9)	26.8 (19.8-51.6)	21.6 (15.1-42.3)	30.3 (8.80-63.1)
Geometric mean	13.5	27.2	22.6	28.1
$AUC_{0-\infty}$ [h*IU/mL]				
N	9	9	9	3
Mean (CV%)	16.3 (36.4)	30.7 (36.4)	25.0 (36.7)	42.5 (27.1)
Median (range)	16.8 (6.89-26.9)	29.0 (20.7-57.4)	22.7 (15.6-46.6)	48.2 (29.2-49.9)
Geometric mean	15.2	29.2	23.8	41.3
CL [mL/h/kg]				
N	9	9	9	3
Mean (CV%)	6.21 (42.0)	5.20 (19.0)	5.57 (13.9)	0.94 (28.1)
Median (range)	4.80 (4.10-11.6)	4.86 (4.29-6.95)	6.04 (4.51-7.01)	0.79 (0.78-1.24)
Geometric mean	5.81	5.13	5.52	0.91
V_{ss} [mL/kg]				
N	9	9	9	3
Mean (CV%)	90.0 (21.6)	84.1 (25.1)	78.5 (18.0)	42.0 (7.1)
Median (range)	95.7 (54.5-111.7)	76.0 (60.2-115.6)	84.0 (55.8-95.7)	41.8 (39.1-45.0)
Geometric mean	87.9	81.8	77.3	41.9

AUC = area under the concentration curve; CL = clearance; C_{max} = maximum plasma concentration; CV = coefficient of variation; FVIII:C = Factor VIII: coagulant activity; IR = incremental recovery; IU = international units; N = number of evaluable subjects; PK = pharmacokinetics; $t_{1/2}$ = half-life; V_{ss} = volume of distribution at steady state; VWF:Ag = von Willebrand factor: antigen; VWF:CB = von Willebrand factor: collagen binding; VWF:RCo = von Willebrand factor: ristocetin cofactor.

Due to dose calculation errors, 3 subjects received incorrect doses and had major PK deviations. For these subjects, the dose calculation was erroneously based in FVIII:C instead of VWF:RCo, which led to administration of higher doses instead of the prescribed dose of 80 IU VWF:RCo/kg (195.6 and 198.2 IU VWF:RCo/kg at initial and repeat PK; 157.3 IU VWF:RCo/kg and 157.4 IU VWF:RCo/kg at initial PK). To

minimize the interference from inaccurate dosing, another set of PK parameters was generated by excluding these 3 subjects. Compared to the full PK dataset, incremental recovery, $t_{1/2}$, Cl, and Vss were similar. AUC and C_{max} were lower compared with the full PK population; this was attributable to the high doses in the 3 excluded subjects.

Comparison of the PK for VWF:RCo, VWF:Ag and VWF:CB obtained in paediatric study CSLCT-BIO-08-52 with PK data obtained in adults in Study CSLCT-BIO-08-54 (Table 4), shows that VWF PK parameters, such as incremental recovery are higher in VWD patients > 12 years, yielding increased Cmax and AUC, in the >12 years population as compared to the >6 and 6 < 12 years population. In line with this, t1/2 generally appears longer in the >12 years population as compared to the <6 years and 6 < 12 years population.

Table 4: Comparison of baseline-adjusted VWF PK parameters by age group (initial administration; studies CSLCT-BIO-08-54 and CSLCT-BIO-08-52)

	Mean (SD)								
	VWF:RCo			VWF:Ag			VWF:CB		
PK parameter [unit]	CSLCT-BIO-08-54 [a]	CSLCT-BIO-08-52		CSLCT-BIO-08-54 [a]	CSLCT-BIO-08-52		CSLCT-BIO-08-54 [a]	CSLCT-BIO-08-52	
	≥12 years	<6 years	6-<12 years [b]	≥12 years	<6 years	6-<12 years [b]	≥12 years	<6 years	6-<12 years [b]
Number of subjects	12	9	5	12	9	5	12	9	5
Dosage [VWF:RCo IU/kg]	80	80	80	80	80	80	80	80	80
Incr. recovery [kg/mL]	0.017 (0.002)	0.013 (0.003)	0.015 (0.003)	0.018 (0.002)	0.013 (0.003)	0.016 (0.003)	0.020 (0.004)	0.013 (0.002)	0.014 (0.002)
Half-life [h] [c]	13.7 (9.2)	12.9 (8.1)	10.4 (1.7)	18.3 (4.0)	12.0 (4.6)	10.8 (1.4)	16.0 (4.6)	10.6 (2.7)	9.67 (2.0)
AUC_{0-t} [h*IU/mL]	17.7 (9.7)	8.86 (4.6)	10.1 (4.7)	37.8 (13.3)	19.5 (7.1)	22.1 (3.6)	24.8 (8.8)	16.2 (3.9)	15.8 (2.8)
MRT [h] [c]	14.0 (5.0)	17.3 (12.3)	11.5 (2.6)	23.6 (5.0)	15.4 (7.0)	13.5 (1.7)	20.0 (4.4)	13.0 (4.0)	12.0 (2.4)
C_{max} [IU/mL]	1.65 (0.63)	1.03 (0.23)	1.18 (0.26)	2.29 (0.59)	1.60 (0.22)	1.83 (0.43)	1.68 (0.50)	1.49 (0.27)	1.42 (0.25)
t_{max} [h] (median [range])	0.25 (0.25 - 1.03)	0.55 (0.50 - 0.62)	0.58 (0.50 - 0.60)	0.25 (0.25 - 1.00)	0.55 (0.50 - 0.62)	0.58 (0.50 - 0.60)	0.25 (0.25 - 1.00)	0.55 (0.50 - 0.62)	0.58 (0.50 - 0.60)
Cl [mL/h/kg] [c]	6.09 (1.66)	8.91 (5.79)	7.33 (1.24)	3.57 (0.69)	6.84 (3.60)	4.83 (0.25)	3.53 (0.89)	7.27 (2.42)	6.28 (0.74)
V_{ss} [L/kg] [c]	0.075 (0.035)	0.103 (0.032)	0.082 (0.011)	0.083 (0.019)	0.089 (0.024)	0.065 (0.007)	0.069 (0.016)	0.087 (0.014)	0.075 (0.016)

AUC = area under the curve; Cl = total clearance; C_{max} = maximum concentration; incr. = incremental; IU = International Units; MRT = mean residence time; PK = pharmacokinetic; SD = standard deviation; t_{max} = time the maximum concentration occurs; V_{ss} = volume of distribution at steady state; VWF = Von Willebrand factor; VWF:Ag = Von Willebrand factor:Antigen; VWF:CB = Von Willebrand factor:Collagen Binding capacity; VWF:RCo = Von Willebrand factor:Ristocetin Cofactor activity.

[a] Excluding Subjects 10008, 22002, and 22003 who had elevated pre-infusion VWF:RCo concentrations (Section 2.7.2.2.2.1.1).

[b] Excluding Subjects 080101, 161106, and 161107 who had received incorrect PK doses (Section 2.7.2.2.2.2.1).

[c] Due to the baseline adjustment in Studies CSLCT-BIO-08-54 and CSLCT-BIO-08-52, results are based on a reduced number of subjects, dependent on study and VWF component.

The VWF and FTVIII PK data in VWD patients < 6 years and 6 years < 12 years were summarised in the SmPC, in order to provide relevant information to prescribers.

Table 5: Baseline-adjusted initial PK parameters of VWF and FVIII:C in subjects <6 (N=9) and 6-12 years old (N=5)

	VWF:RCo				VWF:Ag				VWF:CB				FVIII:C			
parameter	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
	< 6 years		6-12 years		< 6 years		6-12 years		< 6 years		6-12 years		< 6 years		6-12 years	
Incremental recovery (kg/mL)	9	0.013 (0.003)	5	0.015 (0.003)	9	0.013 (0.003)	5	0.016 (0.003)	9	0.013 (0.002)	5	0.014 (0.002)	8	0.021 (0.012)	5	0.017 (0.007)
Half-life (h)	5	12.9 (8.1)	3	10.4 (1.7)	8	12.0 (4.6)	5	10.8 (1.4)	8	10.6 (2.7)	5	9.7 (2.0)	4	19.4 (1.2)	3	17.0 (13.7)
AUC_{0-72} (h*IU/mL)	9	8.9 (4.6)	5	10.1 (4.7)	9	19.5 (7.1)	5	22.1 (3.6)	9	16.2 (3.9)	5	15.8 (2.8)	8	16.4 (7.7)	3	17.7 (14.5)
MRT (h)	5	17.3 (12.3)	3	11.5 (2.6)	8	15.4 (7.0)	5	13.5 (1.7)	8	13.0 (4.0)	5	12.0 (2.4)	4	26.0 (1.9)	3	22.3 (19.7)

C_{max} (IU/mL)	9	1.03 (0.23)	5	1.18 (0.26)	9	1.60 (0.22)	5	1.83 (0.43)	9	1.49 (0.27)	5	1.41 (0.25)	8	0.73 (0.31)	5	0.60 (0.27)
T_{max} (h) †	9	0.55 (0.04)	5	0.56 (0.04)	9	0.55 (0.04)	5	0.56 (0.04)	9	0.55 (0.04)	5	0.56 (0.04)	8	4.25 (7.84)	5	0.56 (0.04)
Total clearance (mL/(h*kg)	5	8.91 (5.79)	3	7.33 (1.24)	8	6.84 (3.60)	5	4.83 (0.25)	8	7.27 (2.42)	5	6.28 (0.74)	4	2.52 (1.13)	3	10.6 (13.5)
V_{ss} (mL/kg)	5	102.8 (32.2)	3	82.3 (10.5)	8	89.0 (24.4)	5	64.8 (6.6)	8	87.4 (14.4)	5	74.9 (15.9)	4	65.2 (27.9)	3	97.4 (42.6)

AUC = area under the curve; C_{max} = maximum plasma concentration; IU = International Unit; MRT = mean residence time; N = number of subjects; SD = standard deviation; t_{max} = time to maximum concentration occurs; V_{ss} = volume of distribution at steady state; VWF:Ag = von Willebrand factor: Antigen; VWF:CB = von Willebrand factor: Collagen Binding; VWF:RCo = von Willebrand factor: Ristocetin Cofactor, FVIII:C = Factor VIII: Coagulant

Population Pharmacokinetic Analyses

In order to characterise the PK of human coagulation FVIII/VWF complex in adult and paediatric populations with VWD PK data obtained from pivotal VWD studies CSLCT-BIO-08-52 and CSLCT-BIO-08-54, were combined in a population PK analyses. Next to the type of VWD, only weight appears to be a significant covariate. Weight was shown a covariate both for V and Cl. When weight is included, age was not a significant covariate. The model was based on data obtained in adults (CSLCT-BIO-08-54) as well as in paediatric patients (Study CSLCT-BIO-08-52).

Model-predicted VWF:RCo exposures vs age were conducted using the population PK model which incorporated weight on CL and V, model-predicted AUC and Cmax were obtained by non-compartmental calculations of model-derived (post-hoc) VWF:RCo concentrations predicted individually for each PK sample time point. Thus, predictions of VWF:RCo exposures for different ages after an initial dose were possible due to the presence of weight in the model. There is a consistent pattern in this relationship when comparing the observed exposures versus age to the model predicted exposures versus weight. In addition, it can be observed that VFW:RCo exposure appeared to modestly decrease when age was less than 6 years old.

2.3.3. Discussion on clinical pharmacology

A paediatric PK, safety, and efficacy study CSLCT-BIO-08-52 in VWD patients was submitted in support of the current application. This paediatric study was compliant with the requirements of the CHMP guideline on the clinical investigation of human plasma-derived VWF products (CPMP/BPWG/220/02) and the guideline on the Core SmPC for human plasma derived VWF (CPMP/BPWG/278/02).

Overall, the pharmacokinetic data in paediatric patients with von Willebrand disease are very similar to those observed in the adult population.

PK of single dose of 80 IU VWF:RCo/kg body weight was evaluated in paediatric subjects less than 12 years of age with severe VWD. Following infusion, peak concentrations of VWF markers (VWF:RCo, VWF:Ag, and VWF:CB) and FVIII:C were achieved immediately with a mean IR of 0.013-0.016 (IU/mL)/(IU/kg) for VWF markers and 0.017-0.021 (IU/mL)/(IU/kg) for FVIII:C. The elimination t1/2 of VWF markers was between 9.7 and 12.9 h whereas FVIII:C had a longer t1/2 of approximately 18 h due to a plateau effect that may represent the net effect of decreasing levels of exogenous FVIII, combined with increasing endogenous FVIII levels. PK parameters from the repeat PK evaluation were similar to those from initial PK. Voncento exposure and disposition were comparable between <6-year-old and 6-12-year-old subjects.

However, PK parameters such as incremental recovery are higher in VWD patients > 12 years, yielding increased Cmax and AUC, in the >12 years population as compared to the <6 and 6- 12 years population. In line with this, t1/2 generally appears longer in the >12 years population as compared to the <6 years and 6-12 years population.

The VWF and FTVIII PK data in VWD patients < 6 years and 6 -12 years are summarised in the SmPC, in order to provide relevant information to prescribers (see section 5.2).

Dosing errors were made in 3 out of 17 paediatric subjects in study CSLCT-BIO-08-52. For these subjects, the dose calculation was erroneously based in FVIII:C instead of VWF:RCo, which led to administration of higher doses instead of the prescribed dose of 80 IU VWF:RCo/kg. The impact of these dosing errors on the PK conclusions appears limited based on the sensitivity analysis conducted. The MAH agreed to include medication errors as a potential risk in the RMP. The risk will be monitored through routine pharmacovigilance, and any new data on the potential risk will be reviewed in the upcoming PSURs (see also RMP).

The population pharmacokinetic model appears to be sufficiently validated and to provide a reasonable description of the VWF:RCo, VWF:Ag and VWF:CB pharmacokinetics. In the observed VWF plasma-concentration time plots, provided in the report for Population PK study RA21020033, it was apparent that the AUC and Cmax seem higher in the adult population as compared to the <12 years population, as noted in in the discussion of Study CSLCT-BIO-08-52. VWF incremental recovery and exposure in the VWD paediatric population <12 years seems to be lower than in VWD patients >12 years.

The provided data confirm that dosing based on weight is appropriate. Further, the predicted exposures are reasonably in line with observed exposures. Dose/kg-normalised AUC and Cmax are somewhat lower in the population <12 years, as compared to the population > 12 years. This lower exposure should be indicated in the SmPC. It is acknowledged that the lower incremental recovery in VWF patients < 12 years supports the higher dose used in this population as compared to the > 12 years population.

Final dosing recommendations based on the above results have been agreed in the SmPC (see also discussion on Clinical Efficacy):

Prophylaxis treatment
For long term prophylaxis in patients with VWD, a dose of 25 - 40 IU VWF:RCo /kg body weight should be considered at a frequency of 1 to 3 times per week. In patients with gastrointestinal bleeds or menorrhagia, shorter dose intervals or higher doses may be necessary. The dose and duration of treatment will depend on the clinical status of the patient, as well as their VWF:RCo and FVIII:C plasma levels.

Paediatric VWD population
Treatment of bleeding
Usually 40 - 80 IU/kg of von Willebrand factor (VWF:RCo) corresponding to 20 - 40 IU FVIII:C/kg of body weight (BW) are recommended in paediatric patients to treat a bleed.

Prophylaxis treatment
Patients aged 12 to 18 years old: Dosing is based on the same guidelines as for adults.
Patients aged <12 years old: Based on results from a clinical trial in which paediatric patients under 12 years of age were shown to have lower exposure of VWF, a prophylactic dose range of 40 – 80 IU VWF:RCo/kg body weight 1 to 3 times a week should be considered. (see Section 5.2).
The dose and duration of treatment will depend on the clinical status of the patient, as well as their VWF:RCo and FVIII:C plasma levels.

2.3.4. Conclusions on clinical pharmacology

The pharmacokinetic data submitted in support of this variation are satisfactory.

The PK analysis, including the data from the 17 subjects <12 years, confirms that VWF incremental recovery and exposure in the VWD paediatric population <12 years is lower than in VWD patients >12 years, supporting the higher prophylactic dose used in this population as compared to the > 12 years population. Recommendations have been included in the SmPC Section 4.2 accordingly.

The VWF and FTVIII PK data in VWD patients < 6 years and 6 years < 12 years are summarised in the SmPC, section 5.2 in order to provide relevant information to prescribers.

2.4. Clinical efficacy

2.4.1. Main studies

CSLCT-BIO-08-54

This was a Phase II/III, multi-centre, open-label study to assess the PK, efficacy, and safety of Voncento in subjects with severe VWD. As pivotal trial for the marketing authorisation of Voncento in VWD, study CSLCT-BIO-08-54 has been described in detail for the MAA. Only information necessary for understanding the claimed extension of the indication to routine prophylaxis are presented in this assessment report.

Altogether, the study consisted of 3 periods:

• Screening period of up to 28 days.

• PK component of up to 183 days (PK subjects).

• Efficacy component with 3 arms:

Arm1 Prophylaxis (only one subject enrolled), Arm 2 On-demand treatment of bleeding events and Arm 3 in which subjects could continue in order to obtain routine prophylaxis after completing Arm 2.

Concerning routine prophylaxis, in study CSLCT-BIO-08-54 one patient was treated from the start with a routine prophylaxis regimen in Arm 1 and 8 subjects from Arm 2 continued into Arm 3 in which they received a routine prophylaxis regimen.

Methods CSLCT-BIO-08-54

Study participants

Main Inclusion criteria

1. Male and female subjects who were at least 12 years of age.

2. Diagnosed with severe VWD where VWF:RCo was <15% at screening (after a minimum of 5 days since last VWF treatment) or the subject had a history of VWF:RCo <10% documented in their medical notes at enrolment.

3. Where DDAVP treatment was ineffective, contraindicated, or not available.

4. Required a VWF product for prophylactic therapy or to control an NSB event.

Main Exclusion criteria

Subjects who fulfilled any of the following criteria were not eligible for inclusion into this study:

<u>For participants of the PK component:</u>

1. Were actively bleeding immediately prior to the initial PK period.

2. Received DDAVP or a VWF product in the 5 days prior to their first dose of study product.

3. Had Type 2B, 2N, or 2M VWD.

For all subjects:

4. Required a VWF product for a planned surgical procedure at enrolment i.e. a planned surgery should not have been the reason for inclusion into the study.

5. Received aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) within 7 days prior to their first dose of study product.

6. Known history of or were suspected to have VWF or FVIII inhibitors.

Assignment to treatment arms

Prophylaxis arm (Arm 1): Subjects who were being treated on a set prophylaxis regimen with a VWF product at the time of study entry, or who were not on a set prophylaxis regimen but in whom prophylaxis treatment was justifiable in the opinion of the investigator, were enrolled into Arm 1 with a final visit after 12 months

On-demand arm (Arm 2): Subjects who were not being treated on a set prophylaxis regimen with a VWF product at the time of study entry,

Arm 3: Subjects, who completed on-demand treatment in Arm 2 and who at the Month 12 visit qualified to be switched to a set prophylactic regimen according to the pre-specified criteria given below entered Arm 3 to receive prophylaxis with Voncento for 12 months.

Eligibility to be switched to Arm 3 was assessed by the investigator using the following criteria as a guideline:

– Joints: either ≥3 spontaneous bleeding events in the same joint or ≥3 spontaneous bleeding events in various joints over a 6-month period.

– Gastrointestinal: >2 gastrointestinal bleeding events over a 12-month period.

– Epistaxis: ≥5 severe epistaxis episodes requiring Voncento treatment or erythrocyte transfusion over a 6-month period.

– Menorrhagia uncontrolled by the contraceptive pill or tranexamic acid.

– More than 1 bleeding event per month at any site requiring Voncento treatment over a 6-month period.

– Investigator's opinion in consultation with the Medical Monitor.

These criteria for continuation into Arm 3 reflect a clinically severe disease profile in patients likely to benefit from routine prophylaxis and are considered to be appropriate.

Treatments

Duration of treatment was 12 months for Arm 1 and Arm 2 and 24 months for those who continued from Arm 2 into Arm 3.

The frequency and dose of administration during the efficacy component was determined by the investigator using the schedule given in Table 6 as a guide.

Table 6. Guidelines for Voncento dosage during the efficacy component

Indication	Dose (IU/kg)		Dose Frequency	Target FVIII / VWF (% or IU/dL)
	FVIII:C	VWF:RCo		
NSB	12.5-25	25-50	Initial	VWF peak level >50%, FVIII >30%
	12.5	25	Subsequent (every 12 to 24 h)	VWF / FVIII trough levels of >30% until bleeding stopped (usually 2 to 4 days)
Prophylaxis	12.5-20	25-40	1 to 3 times weekly	Trough >1%
Prophylaxis for menorrhagia	12.5-25	25-50	On Days 1, 1 and 2 or 1, 2, and 3 per cycle	VWF / FVIII peak levels >30%
Minor surgery	30	60	Daily	VWF / FVIII trough levels of >30% until healing was complete (usually 2 to 4 days)
Major surgery	30-40	60-80	Initial	VWF peak level >100%, FVIII >60%
	15-30	30-60	Subsequent (every 12 to 24 h)	VWF / FVIII trough levels of >50% until healing was complete (usually 5 to 10 days)

FVIII = factor VIII; FVIII:C = factor VIII: coagulant activity; IU = international units; NSB = non-surgical bleeding; VWF = von Willebrand factor; VWF:RCo = von Willebrand factor: ristocetin cofactor.

Objectives

Primary objectives

1. To investigate the initial and repeat PK profile of Voncento in subjects with severe VWD.
2. To assess the haemostatic efficacy of Voncento in subjects with VWD who require a VWF product to control an NSB event.
3. To assess the effectiveness of a prophylaxis regimen as compared to on-demand therapy with Voncento in preventing NSB events.

Secondary objectives

1. To assess the safety of Voncento used both as on-demand therapy to treat NSB events and as prophylactic therapy.
2. To assess the haemostatic efficacy of Voncento for subjects who undergo surgical procedures during the study period.

Outcomes / endpoints

Primary efficacy endpoints include:

- Haemostatic Efficacy assessed as in table 6.
- Blood product transfusion requirements, and the number of treatments/units required to resolve any bleeding event
- VWF:RCo/ FVIII:C concentrate usage: number of infusions, IU/kg per dose, per event, per month and per year.
- Assessment of blood loss during any surgical procedure

- An assessment in the number of spontaneous or traumatic NSB events on a monthly basis and overall

Secondary endpoints include:

1. The nature and incidence of adverse events (including the development of FVIII and/or VWF inhibitors)

2. Assessment of haemostatic efficacy of Voncento in usage for a surgical event according to a 4 point ordinal scale, need for transfusion and assessment of blood loss.

Haemostasis assessment

Clinical efficacy parameters were haemostasis, number of bleeding events, study product usage, blood product transfusion requirements, and surgeon's assessment of blood loss during a surgical procedure.
Haemostasis was to be assessed overall every 3 months by the investigator and monthly by the subject, and for each NSB and surgical event by the investigator and subject.
Overall clinical assessments of haemostatic efficacy were done by the investigator in conjunction with the subject (or legal guardian) based on a 4-point efficacy grading scale outlined in Table 7.

The severity of NSB events was assessed by the investigator as major or minor. Major NSB events included any bleeding into a joint or muscle, or a mucosal bleeding of the gastro-intestinal tract (excluding nasal or oral bleeding). All other NSB events were classified as minor unless the investigator assessment noted otherwise.

Table 7. Efficacy grading scales

Efficacy grade	Definition
Excellent	Haemostasis achieved / cessation of bleeding.
Good	Slight oozing / partial but adequate control of bleeding; does not require additional product for unplanned treatment.
Moderate	Moderate bleeding / moderate control of bleeding; required additional product for unplanned treatment.
None	Severe uncontrolled bleeding.

Sample size

The number of subjects was based on the CHMP guideline [CPMP/BPWG/220/02] which requires at least 12 subjects with VWD to take part in a PK study, 6 of whom should have Type 3 VWD.

Randomisation

The study was uncontrolled.

Blinding (masking)

The study was open label.

Statistical methods

Continuous variables were summarised using descriptive statistics: number of non-missing values, mean, standard deviation (SD), minimum, 25th percentile, median, 75th percentile, and maximum.

The sample size was estimated in line with the Guideline on the Clinical Investigation of Human Plasma Derived von Willebrand Factor Products (CPMP/BPWG/220/02).

Per the statistical analysis plan, no formal statistical tests were to be performed but a descriptive approach to data analysis was used.

Results

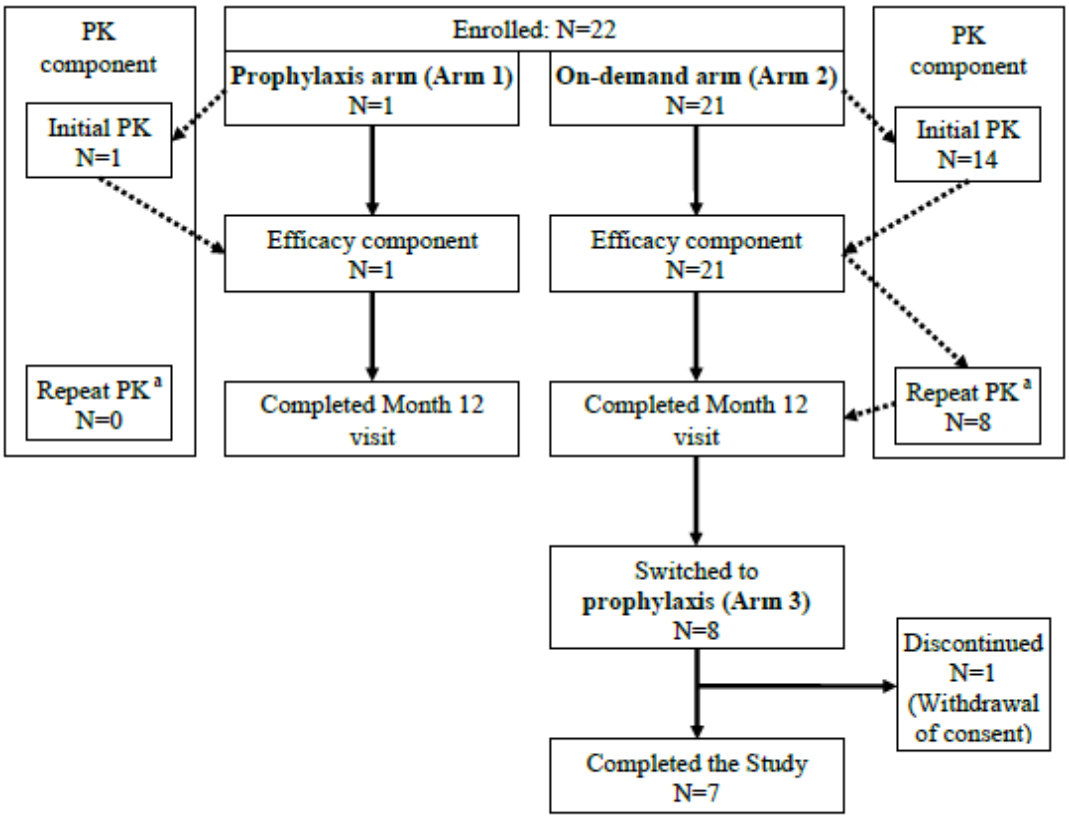
Participant flow

Twenty two (22) patients, including 3 adolescents, were treated in the study thus comprising the safety population. One patient was included in the prophylaxis arm (Arm 1) and 21 in the on demand arm (Arm 2). All patients completed the 12-month visit. The efficacy population used for the efficacy evaluation included all 21 patients who received study drug and had at least 1 NSB after baseline with an available haemostatic efficacy assessment.

Fifteen (15) patients participated in the PK component and 8 of these, all from the on-demand arm (Arm 2) and all with Type 3 VWD, were assessed for the repeat PK evaluation.

Eight (8) patients from on demand Arm 2 (but none of the adolescent subjects) including 6 with Type 3 VWD, entered Arm 3 thus switching to prophylaxis for 12 months. One subject (Type 3 VWD) withdrew his consent and discontinued treatment after 10.5 months in Arm 3. Thus 7 subjects completed the study after 24 months, with 12 months on a prophylaxis regimen.

Figure 1. Patients' disposition



N = number of subjects; PK = pharmacokinetics.

[a] for PK subjects with Type 3 Von Willebrand disease only.

Source: Tables 14.1.1 and 14.1.2

Recruitment

A total of 22 subjects were recruited and received study drug in 6 centres. The first subject enrolled on 30 June 2009. The last subject completed the Month 12 visit on 6 March 2011 and the last subject completed the Month 24 visit on 16 February 2012.

Conduct of the study

There were 3 substantial protocol amendments and 2 protocol deviations which are not considered to have impacted the validity of the efficacy and safety data.

Amendment 3 which was addition of the inclusion criterion of "DDAVP unavailable", while allowing use of Voncento in a real-life situation, may have allowed inclusion of patients with milder bleeding episodes. This was of concern in the assessment for the MAA but it was concluded that the amendment had not negatively impacted the data and that efficacy of Voncento in VWD had been adequately demonstrated.
For the assessment of the data for an indication in routine prophylaxis it is not of relevance as DDAVP would not be used in prophylaxis.

Baseline data

All subjects were Caucasian, 10 (45.5%) were male and 12 (54.5%) female, and the mean age was 33.6 years (range: 15-68 years). Three adolescent subjects (aged 12 - <18 years) participated in Arm 2 of the study (2 subjects aged 15 years and 1 subject aged 16 years and none of them continued into Arm 3.

Table 8. Demographics

Variable	Arm 1 N=1	Arm 2 N=21	Arm 3 N=8	Total N=22
Sex, n (%)				
Male	0	10 (47.6)	6 (75.0)	10 (45.5)
Female	1 (100.0)	11 (52.4)	2 (25.0)	12 (54.5)
Ethnic origin, n (%)				
Caucasian	1 (100.0)	21 (100.0)	8 (100.0)	22 (100.0)
Age [years]				
Mean (SD)	46.0 (-)	33.0 (15.3)	43.0 (15.9)	33.6 (15.2)
Median (range)	46.0 (46 - 46)	28.0 (15 - 68)	42.5 (21 - 68)	30.5 (15 - 68)
<18 years, n (%)	0	3 (14.3)	0	3 (13.6)
≥18 years, n (%)	1 (100.0)	18 (85.7)	8 (100.0)	19 (86.4)
Weight [kg]				
Mean (SD)	75.6 (-)	72.5 (15.39)	81.3 (14.02) [a]	72.6 (15.03)
Median (range)	75.6 (75.6 - 75.6)	70.0 (51.5 - 98.5)	82.5 (61.5 - 98.5) [a]	71.0 (51.5 - 98.5)
Height [cm]				
Mean (SD)	167.0 (-)	168.8 (8.1)	172.3 (7.0)	168.7 (7.9)
Median (range)	167.0 (167 - 167)	168.0 (155 - 182)	174.0 (162 - 180)	168.0 (155 - 182)

n = number of subjects with characteristic; N = total number of subjects; SD = standard deviation.
[a] Body weight measured at Month 12 (start of prophylaxis treatment for Arm 3 subjects).
Source: Tables 14.1.4.1 and 14.3.5.1

Table 9. Von Willebrand disease history in study CSLCT-BIO-08-54

Variable	Arm 1 N=1	Arm 2 N=21	Arm 3 N=8	Total N=22
VWD Type, n (%)				
Type 1	1 (100.0)	4 (19.0)	1 (12.5)	5 (22.7)
Type 2A	0	4 (19.0)	1 (12.5)	4 (18.2)
Type 3	0	13 (61.9)	6 (75.0)	13 (59.1)

Numbers analysed

Efficacy results were based on the efficacy population (treated subjects who had at least 1 NSB event after baseline with an available haemostatic efficacy assessment).
This consisted of 1 subject in Arm 1 (prophylaxis) and 20 subjects in Arm 2 (on-demand) in the first 12 months of the study, and 8 subjects in Arm 3 who received prophylaxis treatment during Months 13-24 (after being treated on-demand in Arm 2).

Outcomes and estimation

Study Drug Dosage

In pivotal study CSLCT-BIO-08-54 the 20 patients in the on-demand arm (Arm 2) had a median number of 20.0 infusions (range: 3-92). The mean (SD) average dose per infusion was 37.8 (8.7) IU VWF:RCo/kg and the median average dose per infusion was 36.1 IU VWF:RCo/kg (range: 29 - 64 IU/kg).

The 8 subjects who later went on to prophylaxis in Arm 3, first received a higher median number of 30.5 infusions (range: 18 92) at a median average dose per infusion of 37.2 IU VWF:RCo/kg (range: 29-46 IU/kg), during their 12 month period of on-demand treatment in Arm 2.

On the prophylaxis regimen in Arm 3, their median number of infusions increased to 72.5 IU (range: 16-118) and the median average dose per infusion decreased to 28.8 IU VWF:RCo/kg.

In prophylaxis treatment Arm 3, their median total prophylaxis dose of IMP was 1843.0 IU VWF:RCo/kg (range: 539.7 - 4110.2 IU/kg).

The one patient included in the prophylaxis arm (Arm 1) participated in the study for 15 months. She received 197 infusions with 37.9 IU VWF:RCo/kg IMP per infusion administered every 2-3 days, and 2 additional infusions of 55.3 and 27.7 IU VWF:RCo/kg, to treat a major mucosal NSB event.
Her total amount of human coagulation FVIII/VWF complex received 7470.7 IU VWF:RCo/kg.

Number of bleeding events during on-demand treatment (Arm 2)

The 20 subjects of Arm 2 reported 533 NSB events during the study, (median 19.5 NSB events per subject, range of 2 to 82 events (Table 9). The majority of NSB events in Arm 2 were spontaneous [99.2%]), minor [76.5%], and mucosal [78.2%]. Eight subjects reported 125 major NSB events.
Six subjects had 126 NSB events that did not require treatment with human coagulation FVIII/VWF complex and which were consequently not assessed for haemostatic efficacy.

Number of bleeding events during prophylaxis (Arm 3 and Arm 1)

Compared to the on-demand treatment, there were very few bleeds experienced by the subjects on prophylaxis. Of the 8 subjects in Arm 3, only 5 subjects reported bleeds. There was a total of 10 bleeds in

these 5 subjects with a median number of 1 event (range: 1-6 events) per subject during prophylaxis compared to 26.5 events (range 18-82) while receiving on-demand treatment in Arm 2.
All 10 NSB events were spontaneous, 7 were minor and 8 were mucosal. Two subjects in Arm 3 experienced a total of 3 major NSB events, including 1 major mucosal NSB event which was a gastrointestinal bleed and was treated with additional Voncento.

The single subject in Arm 1 had a higher number of bleeds on prophylaxis than the subjects in Arm 3, reporting 10 NSB events during her 15-months prophylaxis. All bleeds were spontaneous and mucosal; 2 were minor and 8 major. The subject only treated 1 major mucosal event outside of her prophylaxis regimen with additional human coagulation FVIII/VWF complex.

Table 10. Number of bleeding events in Arm 3 (prophylaxis; N=8) (efficacy population) (study CSLCT-BIO-08-54)

			Number of bleeding events per subject			
Bleeding type	**N**	**n (%)**	**Mean**	**SD**	**Median**	**Min; Max**
All NSB events	5	10 (100.0)	2.0	2.2	1.0	1; 6
Spontaneous	5	10 (100.0)	2.0	2.2	1.0	1; 6
Trauma	0	0	0.0	0.00	0.0	0; 0
Post-surgery	0	0	0.0	0.00	0.0	0; 0
Major	2	3 (30.0)	1.5	0.7	1.5	1; 2
Minor	4	7 (70.0)	1.8	1.5	1.0	1; 4
Joint	1	2 (20.0)	2.0	-	2.0	2; 2
Mucosal	5	8 (80.0)	1.6	1.3	1.0	1; 4
Muscle	0	0	0.0	0.00	0.0	0; 0
Treated at home	5	10 (100.0)	2.0	2.2	1.0	1; 6
Treated at hospital	0	0	0.0	0.00	0.0	0; 0
IMP not needed	0	0	0.0	0.00	0.0	0; 0

IMP = investigational medicinal product; Max = maximum; Min = minimum; n = total number of bleeding events; N = number of subjects with respective event; NSB = non-surgical bleeding; SD = standard deviation.
Source: Section 5.3.5.2.2 (VWD), CSLCT-BIO-08-54, Table 20

The number and type of bleeds experienced in Arm 2 by the 8 subjects who went on to receive prophylaxis is given in Table 11.
During prophylaxis, there were 3 major bleeds in 2 subjects and 1 subject experienced 2 joint bleeds. In comparison, in the same 8 subjects during on-demand treatment, 5 subjects experienced a median of 7.0 major bleeds (range 2 to 59) and 3 subjects experienced a median of 34 joint bleeds (range 7 to 58).

Table 11. Number of bleeding events per patient during on-demand Arm 2 by subgroup (efficacy population) (study CSLCT-BIO-08-54)

	Arm 2 (on-demand; N=20)					
	Arm 2 but not Arm 3 (N=12)			Arm 2 then Arm 3 (N=8)		
Bleeding type	N	Median	Min; Max	N	Median	Min; Max
All NSB events	12	12.0	2; 69	8	26.5	18; 82
Spontaneous	12	12	2; 69	8	26.0	17; 82
Trauma	1	1.0	1; 1	2	1.0	1; 1
Post-surgery	0	-	-	1	1.0	1; 1
Major	3	3.0	3; 3	5	7.0	2; 59
Minor	12	12.0	2; 69	8	20.0	11; 39
Joint	1	2.0	2; 2	3	34.0	7; 58
Mucosal	12	12.0	2; 69	8	20.0	12; 39
Muscle	1	1.0	1; 1	3	2.0	2; 12
Treated at home	8	10.0	3; 20	8	26.0	18; 81
Treated at hospital	10	1.5	1; 4	6	1.0	1; 1
Biostate not needed	6	7.0	1; 65	0	-	-

N = number of subjects with at least 1 bleeding event; Max = maximum; Min = minimum; NSB = non-surgical bleeding.
Source: Tables 14.2.16.1 and 14.2.16.1.1

Haemostatic efficacy in prophylaxis: investigator and subjects' assessment

In Arm 3 (prophylaxis), haemostatic efficacy after treatment with human coagulation FVIII/VWF complex was assessed by the investigator as excellent in the treatment of all 10 NSB events and also generally for all subjects at every 3-month interval.

All subjects in Arm 3 with an available monthly assessment also assessed the haemostatic efficacy of human coagulation FVIII/VWF complex as excellent for each month.

One patient experienced a major spontaneous mucosal bleed in the gastrointestinal tract that lasted for 3 days and was treated with additional human coagulation FVIII/VWF complex. The overall haemostatic efficacy of this event was assessed as excellent by both the investigator and the subject

While receiving on-demand treatment in Arm 2, these 8 subjects had experienced 304 bleeds including 116 major bleeds, 99 joint bleeds and 16 muscle bleeds. Haemostatic efficacy was rated by the investigator as excellent in more than 98% of all bleeds.

The single subject in Arm 1 reported haemostatic efficacy ranging as being usually excellent to moderate over the 15 month period. Only 1 of the 10 bleeds she experienced was treated with additional human coagulation FVIII/VWF complex and efficacy for this event was reported as good by both the investigator and subject. Haemostatic efficacy ranged from excellent to moderate over the 15 month period. Only 1 of the 10 bleeds she experienced was treated with additional human coagulation FVIII/VWF complex and efficacy for this event was reported as good by both the investigator and patient.

Ancillary analyses

The MAH presented an analysis of subjects who switched from on-demand (Arm 2) to prophylaxis treatment (Arm 3) compared to those who did not switch.

The sub-group of patients who went on to routine prophylaxis in Arm 3 had more severe disease as evidenced by the higher median number of bleeding events (26.5, range 18 to 82) of which more than one third were rated as major. In comparison those subjects who did not go on to routine prophylaxis had a lower number of bleeds (median 12, range 2 to 69) and only 9% of bleeds were major. This would be in keeping with the higher proportion of subjects with Type 3 VWD amongst those who went on to receive routine prophylaxis.

It is notable that haemostatic efficacy was more often reported as excellent (98.4% of bleeds) in Arm 2 in those who went on to routine prophylaxis compared to 73.8% of bleeds in those not considered suitable for routine prophylaxis. It can be speculated that this may reflect a choice of the investigator in choosing those who responded well to treatment with Voncento to go on to routine prophylaxis.

Overall it can be concluded that the routine prophylaxis treatment regimen was very successful in preventing all types (i.e. mucosal, joint and muscle) of spontaneous bleeding events.

Study CSLCT-BIO-08-52

This was a Phase III, multi-centre, open-label study to investigate the PK, efficacy, and safety of Voncento in paediatric subjects with VWD in whom treatment with a VWF product was required for prophylactic therapy, haemostatic control during surgery, or control of a non-surgical, spontaneous, or traumatic bleeding event.

The Applicant has submitted the PDCO Opinion on compliance by 20/06/2014 in which study CSLCT-BIO-08-52 was considered to be compliant.

Methods

Study participants

Main Inclusion criteria

Subjects who fulfilled the following criteria were eligible for inclusion:

1. Male and female subjects between 0 and <12 years of age.

2. Subjects who had been diagnosed with VWD Type 1, 2A, or 3.

3. Subjects where DDAVP treatment was ineffective, contraindicated, or not available.

4. Subjects with a VWF:RCo <20% at Screening (after a minimum of 5 days since last VWF treatment) or subjects who had a history of VWF:RCo <10% documented in their medical notes at enrolment.

Main Exclusion criteria

These were essentially the same as for Study CSLCT-BIO-08-54 with the exception that in study CSLCT-BIO-08-54 having Type 2B, 2N, or 2M VWD was an exclusion criterion. However, for this study (CSLCT-BIO-08-52) a diagnosis of VWD Type 1, 2A, or 3 is defined as inclusion criterion.

Treatments

Duration of treatment, either on-demand or prophylaxis was to be 12 months. The frequency and dose of Voncento administration was determined by the investigator. The schedule described in study CSLCT-BIO-08-54 was used to guide dosage.

Objectives

Primary objectives:

• To assess the efficacy of Voncento in paediatric subjects with VWD.

• To investigate the PK profile of Voncento in paediatric subjects with VWD.

Secondary objective:

• To assess the safety of Voncento in paediatric subjects with VWD.

Outcomes / endpoints

Primary endpoints:

• Subjective assessment of haemostatic efficacy of Voncento in its usage with an NSB event, surgical procedure, or use in a prophylaxis regimen.

• PK parameters for each VWF and FVIII were derived from plasma concentration values after an initial single dose of Voncento on Day 1. Parameters were also determined 6 months after the initial dose in Type 3 VWD subjects (repeat PK, recovery study).

• Assessment of response was to include the above assessments as well as haemostasis during surgical procedure, blood loss, and transfusion requirements.

Secondary endpoints listed by severity and relationship to Voncento:

• The nature and incidence of AEs

• The development of FVIII and / or VWF inhibitors.

Haemostasis assessment

Please refer to study CSLCT-BIO-08-54.

Sample size

The number of patients was based on the CHMP guideline CPMP/BPWG/220/02 which requires at least 12 subjects with VWD to take part in the PK study, this number should ensure a minimum of 8 evaluable subjects fulfilling the following conditions:

- At least 3 patients with Type 3 VWD and at least 6 subjects aged between 0 and 6 years.
- At study start, only children of ≥6 years of age were to be included; younger children were included after at least 3 subjects of ≥6 years had been enrolled.
- At least 5 investigational sites were to be involved.

Randomisation

The study was uncontrolled.

Blinding (masking)

The study was open label.

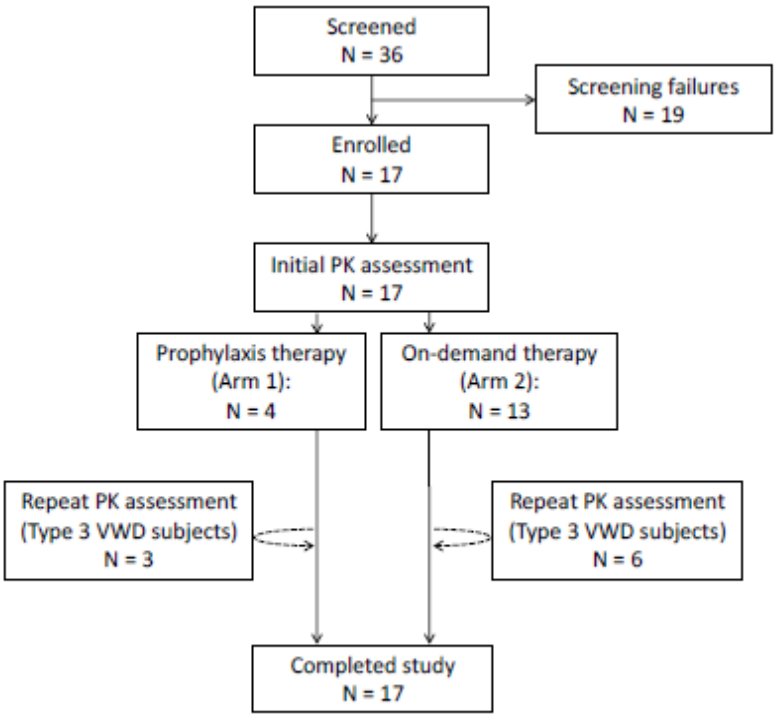
Statistical methods

Descriptive statistics are acceptable as described for Study CSLCT-BIO-08-54.

Results

Participant flow

Figure 2. Subject Disposition



N = number of subjects; PK = pharmacokinetics; VWD = von Willebrand disease.
Source: Tables 14.1.1 and 14.1.2; Listing 16.2.1.1

Recruitment

The first subject enrolled on 29 Jul 2010 and the last subject completed on 27 Aug 2013.

Conduct of the study

There were 1 non-substantial and 2 substantial amendments issued after the study protocol had been finalised on 10 December 2009 and these are not considered to have affected the validity of the data.

Baseline data

The mean age of the 17 patients was 5.2 years with 9 (52.9%) aged <6 years. All but 2 were Caucasian. Demographics were similar between treatment arms with the exception that all 4 patients in prophylaxis Arm 1 were male and a higher proportion of Arm 1 patients (75%) were <6 years old (Table 12).

Overall, 7 patients (41.2%) had Type 2A VWD and the remaining 10 patients had Type 3 VWD, 3 in Arm1 and 7 in Arm 2) (Table 13). One patient was excluded from the efficacy population because he did not experience a NSB.

Table 12. Demographics Study CSLCT-BIO-08-52 (safety population)

Variable	Arm 1 N=4	Arm 2 N=13	Total N=17
Sex, n (%)			
Male	4 (100)	3 (23.1)	7 (41.2)
Female	0	10 (76.9)	10 (58.8)
Ethnic origin, n (%)			
Caucasian	4 (100)	11 (84.6)	15 (88.2)
Black	0	1 (7.7)	1 (5.9)
Hispanic	0	1 (7.7)	1 (5.9)
Age [years]			
Mean (SD)	5.0 (2.5)	5.3 (3.7)	5.2 (3.4)
Median (range)	5.0 (2.0-8.0)	6.0 (0-11.0)	5.0 (0-11.0)
0 to <6 years, n (%)	3 (75.0)	6 (46.2)	9 (52.9)
6 to <12 years, n (%)	1 (25.0)	7 (53.8)	8 (47.1)
Weight [kg]			
Mean (SD)	20.4 (8.2)	22.3 (14.1)	21.9 (12.7)
Median (range)	18.2 (13.0-32.0)	21.0 (7.2-62.0)	18.6 (7.2-62.0)
Height [cm]			
Mean (SD)	113.3 (22.8)	110.4 (24.8)	111.1 (23.7)
Median (range)	109.5 (90.0-144.0)	108.0 (67.0-152.0)	108.0 (67.0-152.0)

n = number of subjects or events with characteristic; N = total number of subjects; SD = standard deviation.

Source: Table 14.1.3

Table 13. Von Willebrand disease history (safety population) (study CSLCT-BIO-08-52)

Variable	Arm 1 N=4	Arm 2 N=13	Total N=17
VWD Type, n (%)			
Type 1	0	0	0
Type 2A	1 (25.0)	6 (46.2)	7 (41.2)
Type 3	3 (75.0)	7 (53.8)	10 (58.8)
Age at first VWD diagnosis			
Mean (SD)	1.8 (0.5)	2.2 (3.0)	2.1 (2.6)
Median (range)	2.0 (1-2)	1.0 (0-10)	1.0 (0-10)
Years since first VWD diagnosis			
Mean (SD)	3.7 (3.0)	3.3 (3.3)	3.4 (3.2)
Median (range)	3.3 (0.4-7.8)	2.2 (0-10.3)	2.3 (0-10.3)
Number of bleeding events per subject in the past 12 months [a]			
Mean (SD)	14.3 (11.0)	3.9 (3.0)	6.4 (7.1)
Median (range)	14.0 (2-27)	2.0 (2-10)	2.0 (2-27)
Classification of previous bleeding events, n (%)			
Number of events	43 (100)	51 (100)	94 (100)
Major	4 (9.3)	17 (33.3)	21 (22.3)
Minor	39 (90.7)	34 (66.7)	73 (77.7)
Response to VWF treatment for previous bleeding events, n (%)			
Number of events	43 (100)	51 (100)	94 (100)
Excellent	35 (81.4)	23 (45.1)	58 (61.7)
Good	6 (14.0)	16 (31.4)	22 (23.4)
Moderate	1 (2.3)	9 (17.6)	10 (10.6)
None	0	0	0
Missing / Unknown	1 (2.3)	3 (5.9)	4 (4.3)

n = number of subjects or events with characteristic; N = total number of subjects; SD = standard deviation; VWD = Von Willebrand disease; VWF = Von Willebrand factor.

[a] The period was <12 months where the subject's VWD diagnosis was <12 months prior to study entry.

Source: Tables 14.1.3 and 14.1.6

Numbers analysed

Efficacy results were based on the efficacy population (treated subjects who had at least 1 NSB event after baseline with an available haemostatic efficacy assessment) that included 16 subjects: 4 subjects in Arm 1 (prophylaxis) and 12 subjects in Arm 2 (on-demand). One subject in Arm 2 was excluded from the efficacy population because he did not experience any NSB events during the study.

Outcomes and estimation

Prophylaxis Regimen

Study Drug Dosage

In Arm 1 (prophylaxis), subjects received a median number of 137.5 infusions at a median average human coagulation FVIII/VWF complex dose of 62.6 IU VWF:RCo/kg per infusion.

In Arm 1, a median of 119 IMP infusions (range: 45-161) were administered as prophylaxis, and a median of 17 (8-41) to treat a bleeding event.
The majority of bleeding events required 1 infusion (71 [78.0%]) of human coagulation FVIII/VWF complex and 18 events [19.8%] required none.

There was a large total number of infusions in Arm 1, including infusions given for prophylaxis and for the treatment of bleeding events. The MAH has confirmed that the mean and median prophylactic doses used in these children were approximately 60 IU/kg and that the frequency of administration ranged from 1 to 3 times a week. (See Table 14 below)

Table 14. Prophylactic frequency and doses in children <12 years old (CSLCT-BIO-08-52

Subject ID	No of infusions /12 months	Frequency of infusions/ week	Mean dose IU/kg (SD)	Median dose IU/kg (range)	Total dose VWF:RCo IU/kg
	94	1.8	45.8 (2.8)	46.2 (42.2 – 50.0)	4326
	161	3.1	66.1 (2.4)	67.1 (62.9 – 68.8)	10641
	45	0.9	58.2 (1.7)	57.1 (54.2 – 60.4)	2622
	144	2.6	64.7 (4.1)	64.9 (49.2 – 77.8)	9333
Mean			58.7 (9.2)	61.5 (46.2 – 67.1)	

Source: Section 5.3.5.2.6 (VWD), CSLCT-BIO-08-52, Listing 16.2.6.4, 16.2.5.1

This median average dose of approximately 60 IU/kg is much higher than the dosage guidance of 25 to 40 IU/kg originally proposed to be recommended for routine prophylaxis for all ages in the SmPC. The PK analysis in the response of the MAH to the RfSI, confirms that VWF incremental recovery and exposure in the VWD paediatric population <12 years is lower than in VWD patients >12 years, supporting the higher dose used in this population as compared to the > 12 years population.

Number of bleeding events

The 4 subjects on prophylaxis experienced a total of 91 NSB, with a median per subject of 23.5 NSB events (Table 15). The majority of these events were spontaneous (79.1%), minor (96.7%), mucosal (87.9%).
There were 3 major NSB events, of which 1 was a major mucosal bleed and there were no surgeries. Eighteen NSB events (19.8%) did not require treatment with human coagulation FVIII/VWF complex and were therefore not assessed for haemostatic efficacy.

Table 15. Number of bleeding events in Arm 1 (prophylaxis; N=4) (efficacy population) (study CSLCT-BIO-08-52)

			Number of bleeding events per subject			
Bleeding type	**N**	**n (%)**	**Mean**	**SD**	**Median**	**Min; Max**
All NSB events	4	91 (100.0)	22.8	13.18	23.5	9; 35
Spontaneous	4	72 (79.1)	18.0	12.91	18.0	5; 31
Trauma	4	19 (20.9)	4.8	3.77	5.0	0; 9
Post-surgery	4	0	0.0	0.00	0.0	0; 0
Major	4	3 (3.3)	0.8	0.50	1.0	0; 1
Minor	4	88 (96.7)	22.0	13.49	22.5	8; 35
Joint	4	3 (3.3)	0.8	0.50	1.0	0; 1
Mucosal	4	80 (87.9)	20.0	12.96	19.0	8; 34
Muscle	4	0	0.0	0.00	0.0	0; 0
Other	4	8 (8.8)	2.0	2.31	2.0	0; 4
Treated at home	4	72 (79.1)	18.0	10.92	16.5	8; 31
Treated at hospital	4	1 (1.1)	0.3	0.50	0.0	0; 1
IMP not needed	4	18 (19.8)	4.5	5.26	3.0	0; 12

IMP = investigational medicinal product; Max = maximum; Min = minimum; n = total number of bleeding events; N = number of subjects with respective event; NSB = non-surgical bleeding; SD = standard deviation.
Source: Section 5.3.5.2.6 [VWD], CSLCT BIO 08 52, Table 15

Three of these 4 subjects were already on a prophylaxis regimen at study entry and had reported very frequent minor or some major bleeding events in their medical history that justified the decision to continue with the prophylaxis regimen during this study.
The number of bleeding events reported during prophylaxis in study CSLCT-BIO-08-52 is actually higher, with a mean and median of approximately 23 bleeds in 12 months, compared to the mean and median of 14 bleeds in the 12 months prior to study entry *(Note: In the response to the RfSI the MAH has clarified that one of these subjects (071105) had been receiving on-demand treatment and not prophylaxis in the 12 months prior to study entry and had experienced 2 bleeds in that time.)*

In the prophylaxis arm, there were 3 major bleeds and 3 joint bleeds in the 4 subjects whereas in the on-demand treatment arm (Arm 2), the 12 subjects experienced 26 major bleeding events (median per subject 2.0 major bleeds [range 0 to 9]) and 11 joint bleeds (median per subject 4.0 [range 0 to 9]).

Compared to the 12 months on a prophylactic regimen prior to entry to study CSLCT-BIO-08-52, the number of bleeding events per individual during the 12 months on Voncento was rather similar in 2 of the 3 subjects concerned (from 28 to 34 and from 19 to 14). It was higher in one subject (from 9 to 35) than in the 12 months prior to study entry.

Haemostatic efficacy in prophylaxis: investigator's and subject's assessment

The haemostatic efficacy for the 73 bleeding events was assessed by the investigator as excellent for 59 events (80.8%) and as good for the remaining 14 events (19.2%) (Table 14). This was also the case for the different types, locations and severities of bleeds, with the exception of the 3 major NSB events, where 1 event (the only major mucosal event) was assessed as excellent and the other 2 (66.7%) as good.
The haemostatic efficacy for each 3-month interval was assessed by the investigator as either excellent (≥50.0% of subjects) or good.

Subjects rated the haemostatic efficacy as excellent for the majority of months during which a bleed occurred and for the majority of bleeding days and as good for the rest.

Overall clinically adequate haemostatic efficacy has been shown in the treatment of breakthrough or traumatic bleeds occurring during prophylaxis and it is noted that for major bleeds and joint bleeds, haemostatic efficacy was rated as good in most cases and rated as excellent in only 1 bleed.

Table 16. Investigator's assessment of haemostatic efficacy per bleeding event in Arm 1 (prophylaxis; N=4) (study CSLCT-BIO-08-52)

		Number (%) of NSB events [a]			
Bleeding type	**Number of NSB events**	**Excellent**	**Good**	**Moderate**	**None**
All NSB events	73	59 (80.8)	14 (19.2)	0	0
Spontaneous	59	49 (83.1)	10 (16.9)	0	0
Trauma	14	10 (71.4)	4 (28.6)	0	0
Post-surgery	0	0	0	0	0
Major	3	1 (33.3)	2 (66.7)	0	0
Minor	70	58 (82.9)	12 (17.1)	0	0
Joint	3	0	3 (100.0)	0	0
Mucosal	62	53 (85.5)	9 (14.5)	0	0
Muscle	0	0	0	0	0
Other	8	6 (75.0)	2 (25.0)	0	0

NSB = non-surgical bleeding; N = number of subjects.

[a] Percentages were based on the number of bleeding events of the considered type with available investigator's assessment. Bleeding events with missing investigator's assessment for efficacy or for which no human coagulation FVIII/VWF complex treatment was needed were not considered for this table.

Source: Section 5.3.5.2.6 [VWD], CSLCT-BIO-08-52, Table 17

The haemostatic efficacy per individual was also provided.

For 2 of the subjects on prophylaxis during study CSLCT-BIO-08-52, no treatment was required for approximately one third of their minor bleeds and for one subject 9% of the minor bleeds did not need treatment. Overall, a higher percentage of bleeds did not require treatment with Voncento in patients on prophylaxis compared to patients receiving only on-demand trteatment where is was 16.7% of bleeds (see below). The one subject who needed additional treatment for all minor bleeds during prophylaxis was receiving a prophylactic dose of 46 IU/kg VWF:RCo twice weekly, but had only experienced 8 minor bleeds. (See Table 17 below)

Table 17. The number and type of bleeding events, 12 months prior to the study, and during the study (CSLCT-BIO-08-52) with haemostatic efficacy by event type

Subject ID	VWD Type	Historical data 12 months prior to study		Voncento Data 12 months during study				
						Haemostatic efficacy (%)		
		Bleed Type	No. of bleeds	Bleed Type	No. of bleeds	Excellent	Good	NT
	3	Major	2	Major	1	0	100	-
		Minor	0	Minor	8	37.5	62.5	
	3	Major	1	Major	1	0	100	0
		Minor	27	Minor	33	84.8	6.1	9.1
	3	Major	2	Major	1	100	0	0
		Minor	17	Minor	13	46.2	23.1	30.7
	2A	Major	5	Major	0	0	100	0
		Minor	4	Minor	35	60.0	2.8	34.3

Source: Section 5.3.5.2.6 (VWD), CSLCT-BIO-08-52 Listing 16.2.6.8. NT = no treatment needed

On-demand Regimen

The mean (± s.d.) number of bleeds in the 12 subjects in Arm 2 (on-demand) of paediatric Study CSLCT-BIO-08-52 in patients <12 years was 8.0 (±6.4) and the median was 5.5 (range 1 to 22) (Table 18).

Table 18. Number of bleeding events in Arm 2 (on-demand; N=12) (efficacy population) (study CSLCT-BIO-08-52)

			Number of bleeding events per subject			
Bleeding type	**N**	**n (%)**	**Mean**	**SD**	**Median**	**Min; Max**
All NSB events	12	96 (100.0)	8.0	6.42	5.5	1; 22
Spontaneous	12	74 (77.1)	6.2	5.39	5.0	0; 21
Trauma	12	22 (22.9)	1.8	2.21	1.0	0; 7
Post-surgery	12	0	0.0	0.00	0.0	0; 0
Major	12	26 (27.1)	2.2	2.55	2.0	0; 9
Minor	12	70 (72.9)	5.8	5.36	3.5	1; 20
Joint	12	11 (11.5)	0.9	2.57	0.0	0; 9
Mucosal	12	79 (82.3)	6.6	5.52	5.0	1; 22
Muscle	12	2 (2.1)	0.2	0.39	0.0	0; 1
Other	12	4 (4.2)	0.3	0.89	0.0	0; 3
Treated at home	12	51 (53.1)	4.3	5.89	2.0	0; 20
Treated at hospital	12	29 (30.2)	2.4	4.76	1.0	0; 17
IMP not needed	12	16 (16.7)	1.3	2.67	0.0	0; 9

IMP = investigational medicinal product; Max = maximum; Min = minimum; n = total number of bleeding events; N = number of subjects; NSB = non-surgical bleeding; SD = standard deviation.
Percentages are based on the total number of bleeding events.
Source: Section 5.3.5.2.6 [VWD], CSLCT-BIO-08-52, Table 19

Study Drug Dosage

In Arm 2, subjects received overall a median number of 8.0 infusions at a median average human coagulation FVIII/VWF complex dose of 50.9 IU VWF:RCo/kg per infusion. *(The assessor concludes that his median dose apparently includes the dose given for PK assessment (n=13).)* In the response to the RfSI, the MAH has clarified the doses given only for the treatment of bleeds.
The mean (± s.d.) number of bleeds in the 12 subjects in Arm 2 of paediatric Study CSLCT-BIO-08-52 in patients <12 years was 8.0 (±6.4) and the median was 5.5 (range 1 to 22) (Table 15).
The per patient mean dose actually used for the treatment of bleeding in the on-demand arm (n=12) of paediatric Study CSLCT-BIO-08-52 in patients <12 years ranged from approximately 35 to 70 IU/kg VWF:RiCo and the per patient median dose ranged from approximately 30 to 80 IU/kg VWF:RiCo. Over all the 12 subjects, the average dose (± s.d.) was 47.6 (± 16.8) IU/kg VWF:RiCo and the median dose was 40.8 (range 30.2 to 88.6) IU/kg VWF:RiCo (See Table 19 below).

These doses are within the range of 40 to 80 IU/kg currently recommended in the Voncento SmPC for the treatment of bleeding and which the MAH also proposes for the paediatric population.

Table 19. On demand doses in children <12 years old (CSLCT-BIO-08-52)

Subject ID	Number of infusions for NSBs	Mean dose IU/kg (SD)	Median dose IU/kg (range)	Total dose VWF:RCo IU/kg
	6	56.6 (4.0)	58.2 (48.4-58.2)	339
	51	37.6 (13.3)	30.2 (24.0-60.4)	1920
	6	46.1 (17.7)	45.0 (30.0-63.3)	277
	3	69.7 (19.0)	80.0 (47.8-81.3)	209
	1	88.6	88.6	89
	22	34.3 (2,3)	34.9 (29.1-36.1)	755
	10	37.6 (0.7)	37.8 (36.4-38.1)	376
	10	36.1 (2.6)	37.6 (31.5-37.6)	361
	7	34.2 (1.6)	34.3 (30.8-35.3)	240
	2	35.9 (4.0)	35.9 (33.1-38.7)	72
	4	43.3 (2.9)	43.7 (40.0-45.7)	173
	3	51.1 (12.0)	45.7 (42.9-64.9)	153
Group Mean/ Median	10.4 (14.0)	47.6 (16.8)	40.8 (30.2-88.6)	414 (508)

Section 5.3.5.2.3 (VWD), CSLCT-BIO-08-52, Listings 16.2.6.4, 16.2.5.1.1;
Subject 161112 received only an initial PK infusions, he did not have a NSB during the study as was exclude from the efficacy analyses

In Arm 2, the majority of bleeding events were treated with only 1 infusion (55 [57.3%]) and 16 events [16.7%] were not treated with human coagulation FVIII/VWF. 25 NSB events (26.0%) required >1 infusion.

Haemostatic efficacy in on-demand treatment: investigator's and subject's assessment

Haemostatic efficacy was assessed by the investigator for all the 80 events as excellent for 36 events (45.0%) and as good for the remaining 44 events (55.0%) (Table 16). This was also the case for the different types, locations and severities of bleeds with the exception of the 11 joint bleeding events, where the haemostatic efficacy of a relatively higher proportion of events was assessed as good (81.8%).

For each 3-month interval, the haemostatic efficacy was assessed by the investigator as either excellent or good.

The haemostatic efficacy was assessed by the subject as excellent for 33 bleeding days (60.0%), as good for 12 bleeding days (21.8%), and as moderate for the remaining 10 bleeding days (18.2%) . There were 13 major mucosal bleeds in 5 subjects. The overall haemostatic efficacy for these 13 events was assessed by the investigator as excellent for 9 cases and as good for 4 cases. The subjects rated the haemostatic efficacy as excellent for the same 9 events and as good for the remaining 2 events, for which a subject assessment is available.

Table 20. Investigator's assessment of haemostatic efficacy per bleeding event in Arm 2 (on-demand; N=12) (study CSLCT-BIO-08-52)

		Number (%) of NSB events [a]			
Bleeding type	**Number of NSB events**	**Excellent**	**Good**	**Moderate**	**None**
All NSB events	80	36 (45.0)	44 (55.0)	0	0
Spontaneous	62	26 (41.9)	36 (58.1)	0	0
Trauma	18	10 (55.6)	8 (44.4)	0	0
Post-surgery	0	0	0	0	0
Major	26	13 (50.0)	13 (50.0)	0	0
Minor	54	23 (42.6)	31 (57.4)	0	0
Joint	11	2 (18.2)	9 (81.8)	0	0
Mucosal	65	30 (46.2)	35 (53.8)	0	0
Muscle	1	1 (100.0)	0		
Other	3	3 (100.0)	0	0	0

NSB = non-surgical bleeding; N = number of subjects.

[a] Percentages were based on the number of bleeding events of the considered type with available investigator's assessment. Bleeding events with missing investigator's assessment for efficacy were not considered for this table. Bleeding events for which no human coagulation FVIII/VWF complex treatment was needed were not considered for this table.

Ancillary analyses

Examination of subgroups

Age group (<6 years versus ≥6 years)

The efficacy population included 8 subjects each in the subgroup of <6-year-old subjects (3 in Arm 1 and 5 in Arm 2) and that of ≥6-year-old subjects (1 in Arm 1 and 7 in Arm 2).

As in the overall efficacy population, in both age subgroups, the haemostatic efficacy was assessed by the investigator as either excellent or good for each 3-month interval and for each NSB event treated with Voncento (Table 21).

Table 21. Investigator's assessment of haemostatic efficacy per bleeding event by treatment arm and age subgroup (efficacy population)

	Arm 1 N = 4						Arm 2 N = 12					
	Age < 6 years (N=3)			Age ≥ 6 years (N=1)			Age < 6 years (N=5)			Age ≥ 6 years (N=7)		
		No.(%) of NSB events			No.(%) of NSB events			No.(%) of NSB events			No.(%) of NSB events	
	n	Excellent	Good	n	Excellent	Good	n	Excellent	Good	N	Excellent	Good
All NSB events	43	31 (73.8)	11 (26.2)	31	28 (90.3)	3 (9.7)	33	16 (48.4)	17 (51.5)	47	20 (42.6)	27 (57.4)

N = number of subjects; NSB = non-surgical bleeding.
Note: Percentages were based on the number of bleeding events of the considered type with available investigator's assessment. Bleeding events with missing investigator's assessment for efficacy were not considered for this table. Bleeding events for which no Voncento treatment was needed were not considered for this table.
Source: Table 14.2.3.1

In Arm 1, the distribution of efficacy ratings of excellent and good across bleeding event categories (spontaneous, trauma, post-surgery, major, minor, joint, mucosal, muscle and other) was similar between age subgroups (Table 24) and also compared to the overall efficacy population (Table 17 and Table 21, respectively).

In Arm 2, the distribution of efficacy ratings of excellent and good across bleeding event categories was also similar between age subgroups with the exception of traumatic bleeds (80% excellent haemostatic efficacy rating in children < 6 years compared to 46.2% in children aged ≥ 6 years) and major bleeds (80% excellent haemostatic efficacy rating in children < 6 years compared to 31.3 % in children aged ≥ 6 years).
For major and traumatic bleeds, there seems to be higher haemostatic efficacy in children < 6 years than in children ≥ 6 years but considering the small populations and potential inter-individual variation in pharmacokinetics no great significance can de attached to this observation.

VWD type (Type 2A versus Type 3)

The efficacy population included 7 subjects with VWD Type 2A (1 in Arm 1 and 6 in Arm 2) and 9 subjects with VWD Type 3 (3 in Arm 1 and 6 in Arm 2).
As in the overall efficacy population, in both VWD type subgroups, the haemostatic efficacy was assessed by the investigator as either excellent or good for each 3-month interval and for each NSB event treated with Voncento (Table 22).
Also, for both VWD Type 2A and Type 3, the haemostatic efficacy was assessed by the subject as either excellent or good for each study month.

Table 22. Investigator's assessment of haemostatic efficacy per bleeding event by treatment arm and VWD Type subgroup (efficacy population)

	Arm 1 (N=4)						Arm 2 (N=12)					
	VWD Type 2A (N=1)			VWD Type 3 (N=3)			VWD Type 2A (N=6)			VWD Type 3 (N=6)		
		No. (%) of NSB events			No. (%) of NSB events			No. (%) of NSB events			No. (%) of NSB events	
Bleeding type	n	Excellent	Good	n	Excellent	Good	n	Excellent	Good	n	Excellent	Good
All NSB events	23	21 (91.3)	2 (8.7)	50	38 (76.0)	12 (24.0)	38	16 (42.1)	22 (57.9)	42	20 (47.6)	22 (52.4)
Spontaneous	21	20 (95.2)	1 (4.8)	38	29 (76.3)	9 (23.7)	35	14 (40.0)	21 (60.0)	27	12 (44.4)	15 (55.6)
Trauma	2	1 (50.0)	1 (50.0)	12	9 (75.0)	3 (25.0)	3	2 (66.7)	1 (33.3)	15	8 (53.3)	7 (46.7)
Post-surgery	0	0	0	0	0	0	0	0	0	0	0	0
Major	0	0	0	3	1 (33.3)	2 (66.7)	8	6 (75.0)	2 (25.0)	18	7 (38.9)	11 (61.1)
Minor	23	21 (91.3)	2 (8.7)	47	37 (78.7)	10 (21.3)	30	10 (33.3)	20 (66.7)	24	13 (54.2)	11 (45.8)
Joint	1	0	1 (100.0)	2	0	2 (100.0)	1	1 (100.0)	0	10	1 (10.0)	9 (90.0)
Mucosal	22	21 (95.5)	1 (4.5)	40	32 (80.0)	8 (20.0)	37	15 (40.5)	22 (59.5)	28	15 (53.6)	13 (46.4)
Muscle	0	0	0	0	0	0	0	0	0	1	1 (100.0)	0
Other	0	0	0	8	6 (75.0)	2 (25.0)	0	0	0	3	3 (100.0)	0

N = number of subjects; NSB = non-surgical bleeding.
Note: Percentages were based on the number of bleeding events of the considered type with available investigator's assessment. Bleeding events with missing investigator's assessment for efficacy were not considered for this table. Bleeding events for which no Biostate treatment was needed were not considered for this table.
Source: Table 14.2.3.1

In subjects with Type 2A VWD, all except 2 bleeds that occurred in the single subject on prophylaxis in Arm 1 were minor mucosal bleeds (see table). In the 6 subjects with Type 2A VWD receiving on-demand treatment in Arm 2, the majority of bleeds were also minor mucosal bleeds (30/38 events) but it is of note that 8/38 events were major mucosal bleeds.
In Arm 2, Type 3 subjects in contrast to with Type 2A, had a higher frequency of traumatic bleeds (15/42, 36% vs 3/38, 8%), of major bleeds (18/42, 43% vs 8/38,21%) and of joint bleeds (10/42, 24% vs 1/38, 3%) with correspondingly less mucosal bleeds. This pattern of type of bleeds matches that expected from current knowledge of VWD sub-types.

Importantly, efficacy was rated as excellent for 9 of 13 major mucosal bleeds, which are often difficult to treat, in subjects with Type 2A VWD.

Summary of main studies

The following tables 23 and 24 summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Von Willebrand Disease

Table 23: Summary of efficacy for Study CSLCT-BIO-08-54

Title: An Open-label Multi-centre Study to Assess the Pharmacokinetics, Efficacy and Safety of Voncento in Subjects with Von Willebrand Disease.		
Study identifier	CSLCT-BIO-08-54	
Design	This is a Phase II/III, multicentre, open-label, uncontrolled study to assess the PK, efficacy, and safety of Voncento in subjects with severe VWD. **Main Inclusion criteria were:** -Male and female subjects ≥12 years of age, -Severe VWD where VWF:RCo was <15% at screening (after a minimum of 5 days since last VWF treatment) or the subject had a history of VWF:RCo <10% documented in their medical notes at enrolment. -DDAVP treatment was ineffective, contraindicated, or not available. -Patients requiring a VWF product for prophylactic therapy or to control an NSB event. Altogether, the study consisted of 3 periods: **1. Screening period** of up to 28 days. **2. PK component** of up to 183 days (PK subjects), which consisted of: A single dose of Voncento on Day 1 A repeat single dose of Voncento on Day 180, at least 6 months after the initial infusion (repeat PK for Type 3 VWD PK subjects only). PK samples were collected on Days 1, 2, 3, and 4, and on Days 180, 181, 182, and 183. All PK subjects were to enter the efficacy component of the study at the completion of the initial PK period. **3. Efficacy component with 3 arms** of up to 12 or 24 months; depending on the treatment arm subjects participated in.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 months not applicable not applicable
Hypothesis	There is no comparator arm or statistical comparison with historical or bibliographic data	
Treatments groups	Arm 1: prophylaxis arm	Routine prophylaxis with Voncento 2 to 3 times per week for 12 months Only 1 subject included
	Arm 2: on-demand arm	On-demand treatment of bleeds for 12 months 20 subjects included
	Arm 3: Switch to prophylaxis Ongoing at time of reporting	Subjects, who completed on-demand therapy with Voncento in Arm 2 and who at the Month 12 visit qualified to be switched to a set prophylactic regimen for an additional 12 months. 8 subjects were enrolled in Arm 3.

Endpoints and definitions for Arm 2 only	Primary endpoint	Haemostatic Efficacy	-Subject and Investigator assessment of haemostatic efficacy at time of each bleeding event. -Retrospective Investigator assessment of haemostatic efficacy performed at the 3 monthly study visit. -Assessment of haemostatic efficacy by the Subject and Investigator using a scale of Excellent, Good, Moderate, None. -Blood product transfusion requirements, and the number of treatments/units required to resolve any bleeding event -VWF:RCo/ FVIII:C concentrate usage: number of infusions, IU/kg per dose, per event, per month and per year. -Assessment of blood loss during surgical procedure -The number of spontaneous or traumatic NSB events on a monthly basis and overall
	Secondary endpoint	Safety in on-demand and prophylactic therapy.	- The nature and incidence of adverse events
	Secondary endpoint	Haemostatic efficacy in surgery	- Assessment of haemostatic efficacy in usage for a surgical event according to a 4 point ordinal scale, need for transfusion and assessment of blood loss.
Database lock	<date>		

Results and Analysis Only the main results are summarized here

Analysis description	**Primary Analysis**
Analysis population	Efficacy results were based on the efficacy population (treated subjects who had at least 1 NSB event after baseline with an available haemostatic efficacy assessment) that included 1 subject in Arm 1 (prophylaxis) and 20 subjects in Arm 2 (on-demand) in the first 12 months of the study, and 8 subjects in Arm 3 who received prophylaxis treatment during Months 13-24 (after being treated on-demand in Arm 2).

Primary Analysis

On-demand Arm 2

Investigator's assessment of haemostatic efficacy per bleeding event

There was a haemostatic efficacy assessment in 407 of 533 events as follows:
Excellent in 375/407 (92.1%); Good in 25/407 (6.1%); Moderate in 7/407 (1.7%)

Subject's assessment of haemostatic efficacy per day of bleeding event, all days

Excellent in 480/606 (79.1%); Good in 104/606 (17.2%); Moderate in 21/606 (3.5%).
For 1 bleeding day (0.2%), the subject assessed the haemostatic efficacy as "none"

Number of Bleeding Events During the Study: Total number and number per subject

The 20 subjects of Arm 2 (on-demand) reported a total of 533 NSB events during the study, The majority of NSB events were spontaneous (529 [99.2%]), minor (408 [76.5%]), mucosal (417 [78.2%]), and were treated at home (381 [71.5]).
In Arm 2, 8 subjects experienced a total of 125 major NSB

Prophylaxis Arm 2

Investigator's assessment of haemostatic efficacy per bleeding event

For all 10 NSB events in Arm 3, excellent haemostatic efficacy after treatment with human coagulation FVIII/VWF complex was reported by the investigator

Subject's assessment of haemostatic efficacy per day of bleeding event, all days

The haemostatic efficacy was assessed as excellent by the subjects for all bleeding days.

Number of Bleeding Events During the Study: Total number and number per subject

Of the 8 subjects in Arm 3 (prophylaxis), 5 subjects experienced NSB events; 1 subject had 6 events and the remaining 4 subjects 1 event each . All 10 events were spontaneous and treated at home; 7 were minor and 8 were mucosal. Two subjects in Arm 3 experienced a total of 3 major NSB events, including 1 major mucosal NSB event.

Prophylaxis Arm 1 patient

The single subject in Arm 1 reported 10 NSB events all of which were spontaneous and mucosal; 2 were minor and 8 major.
Only 1 of these 10 events. a major mucosal event, was treated with additional FVIII/VWF complex at home and the haemostatic efficacy for this event was reported as good by both the investigator and subject.

Blood Transfusion

Only 1 subject in the efficacy population required any blood product transfusion:
An 18-year-old female required 600 mL of packed RBCs each for 2 cases of major uterine bleeding.

	Arm 1 (n=1) Prophylaxis 15 months	Arm 2 (n=20) On-demand 12 months	Arm 3 (n=8) Prophylaxis 12 months
Median number of bleeding events	10	19.5	1.0
Range	Only one subject	2 - 82	1 - 6
Median Number of infusions	197	20.0	72.5
Range	Only one subject	3 - 92	16 – 118

	Median average dose per infusion (IU/kg)	37.9	36.1	28.8
	Range	Only one subject	29 - 64	25 - 35

Table 24: Summary of efficacy for Study CSLCT-BIO-08-52

Title: A Phase III Open-label, Multi-centre Study to Assess the Pharmacokinetics, Efficacy, and Safety of Voncento in Paediatric Subjects with von Willebrand Disease.		
Study identifier	CSLCT-BIO-08-52	
Design	This was a Phase III, multi-centre, open-label study to investigate the PK, efficacy, and safety of Voncento in paediatric subjects with VWD. **Main Inclusion criteria were:** 1. Male and female subjects between 0 and <12 years of age. 2. Subjects who had been diagnosed with VWD Type 1, 2A, or 3. 3. Subjects where DDAVP treatment was ineffective, contraindicated, or not available. 4. Subjects with a VWF:RCo <20% at Screening (after a minimum of 5 days since last VWF treatment) or subjects who had a history of VWF:RCo <10% documented in their medical notes at enrolment.. Altogether, the study consisted of 3 periods: 1. **Screening period** of up to 35 days. 2. **PK period** consisting of 2 parts: • Part 1 (initial PK): single dose of Voncento on Day 1. PK samples collected on Days 1, 2, and 3. • Part 2 (repeat PK): recovery study in Type 3 VWD subjects to occur 6 months after Part 1. On completion of Part 1 of the PK component, all subjects were to immediately enter the treatment period of the study. 3. **Treatment period** (efficacy component with 2 arms) of up to 12 months.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 months not applicable not applicable
Hypothesis	There is no comparator arm or statistical comparison with historical or bibliographic data	
Treatments groups	Arm 1: prophylaxis arm	**Routine prophylaxis:** Subjects who were treated on a set prophylaxis regimen with a VWF product at the time of study entry were enrolled into the prophylaxis arm to receive Voncento as a pre-defined prophylaxis regimen determined by the severity of their disease for a period of 12 months. 4 subjects enrolled
	Arm 2: on-demand arm	On-demand: Subjects who were not treated on a set prophylaxis regimen with a VWF product at the time of study entry were enrolled to start Voncento on-demand treatment of NSB events. 13subjects enrolled

Endpoints and definitions for Arm 2 only	Primary endpoint	Haemostatic Efficacy	-Subject and Investigator assessment of haemostatic efficacy at time of each bleeding event. -Retrospective Investigator assessment of haemostatic efficacy performed at the 3 monthly study visit. -Assessment of haemostatic efficacy by the Subject and Investigator using a scale of Excellent, Good, Moderate, None. -Blood product transfusion requirements, and the number of treatments/units required to resolve any bleeding event -VWF:RCo/ FVIII:C concentrate usage: number of infusions, IU/kg per dose, per event, per month and per year. -Assessment of blood loss during surgical procedure -The number of spontaneous or traumatic NSB events on a monthly basis and overall.
	Secondary endpoint	Safety in on-demand and prophylactic therapy.	- The nature and incidence of adverse events - The development of FVIII and / or VWF inhibitors.
Database lock	<date>		

Results and Analysis Only the main results are summarized here

Analysis description	**Primary Analysis**
Analysis population	Efficacy results were based on the efficacy population (treated subjects who had at least 1 NSB event after baseline with an available haemostatic efficacy assessment) that included 16 subjects: 4 subjects in Arm 1 (prophylaxis) and 12 subjects in Arm 2 (on-demand). One subject in Arm 2 was excluded from the efficacy population because he did not experience any NSB events during the study

Primary Analysis

On-demand Arm 2

Investigator's assessment of haemostatic efficacy per bleeding event

There was a haemostatic efficacy assessment in all 80 events as follows:
Excellent in 36/80 (45.0%); Good in 44/80 (55.0%).

Subject's assessment of haemostatic efficacy per day of bleeding event, all days

Excellent for 33/55 bleeding days (60.0%), good for 12/55 bleeding days (21.8%), and moderate for the remaining 10 bleeding days.

Number of Bleeding Events During the Study: Total number and number per subject

The 12 subjects of Arm 2 (on-demand) experienced a total of 96 NSB events. The majority were spontaneous (77.1%), minor (72.9%), mucosal (82.3%), and were treated at home (53.1%). A total of 26 events (27.1%) were considered major, including 13 major mucosal NSB events. Sixteen NSB events (16.7%) did not require treatment with human coagulation FVIII/VWF complex; these events were therefore considered not evaluable and consequently not assessed for haemostatic efficacy.

Prophylaxis Arm 1

Investigator's assessment of haemostatic efficacy per bleeding event

The haemostatic efficacy for the 73 bleeding events treated with human coagulation FVIII/VWF complex was assessed by the investigator as excellent for 59 events (80.8%) and as good for the remaining 14 events (19.2%)

Subject's assessment of haemostatic efficacy per day of bleeding event, all days

The haemostatic efficacy was assessed as excellent for 60/76 bleeding days (78.9%) and as good for the remaining 16 bleeding days (21.1%).

Number of Bleeding Events During the Study: Total number and number per subject

The 4 subjects in Arm 1 (prophylaxis) experienced a total of 91 NSB events, The majority of these events were spontaneous (79.1%), minor (96.7%), mucosal (87.9%), and treated at home (79.1%); 3 events (3.3%) were major, of which 1 event was a major mucosal NSB event.

<u>Blood Transfusion</u>

No subjects in study CSLCT-BIO-08-52 required blood product transfusions during the treatment period.

	Arm 1 (n=4) 12 months	Arm 2 (n=12) 12 months	
Median number of bleeding events	23.5	5.5	
Range	9 - 35	1 - 22	
Median Number of infusions	137.5 Prophylax: 119 NSB: 17	8.0	
Range	55 - 205 Prophylax: 45 –161 NSB: 8 - 41	(1-53)	
Median average dose per infusion (IU/kg)	62.6	50.9	

	Range	(46.7-66.5)	(35.4-115.1)	

Analysis performed across trials (pooled analyses and meta-analysis)

Prospective studies CSLCT-BIO-08-54 (adults and adolescents), CSLCT-BIO-08-52 (paediatrics below 12 years of age), and CSLCT-BIO-03-97 (adults and children) provide efficacy data on the treatment of VWD with human coagulation FVIII/VWF complex both as prophylaxis and on demand therapy:

Prophylaxis therapy:
9 subjects (Arms 1 and 3) in study CSLCT-BIO-08-54;
4 subjects (Arm 1) in study CSLCT-BIO-08-52;
4 subjects in CSLCT-BIO-03-97.

On-demand therapy:
20 subjects (Arm 2) in study CSLCT-BIO-08-54;
12 subjects (Arm 2) in study CSLCT-BIO-08-52;
19 subjects in CSLCT-BIO-03-97.

Study CSLCT-BIO-03-97 mainly provides efficacy data on the treatment for surgical events and supportive data from 4 subjects receiving prophylaxis treatment.
The investigator-led studies provide supportive information on the treatment of VWD with human coagulation FVIII/VWF complex as on-demand therapy. The Shortt study contributes supportive data on surgical events in adults and the Howman study supportive data on NSB and surgical events in paediatric patients.

Prophylaxis Regimen

The data from study CSLCT-BIO-08-52 and CSLCT-BIO-08-54 provide a comparison between prophylaxis in children < 12 years old and adults. There are no data on prophylaxis in the paediatric population aged ≥12 years to 18 years.

Number of Non-surgical Bleeding Events

There were considerably more bleeding events during prophylaxis reported in paediatric study CSLCT-BIO-08-52 (91 events in 4 subjects; median 23.5, range 9 to 35) than in the adults on prophylaxis in study CSLCT-BIO-08-54 (10 events in 8 subjects in Arm 3; median 1.0, range 1 to 6). The single subject in Arm 1 reported 10 bleeds over 12 months (Table 21).
In the prophylaxis arm of paediatric study CSLCT-BIO-08-52, there were 3 major bleeds in the 4 subjects (one major bleed in each of 3 subjects) and 3 joint bleeds in the 4 subjects.
For comparison, in prophylaxis Arm 3 of study CSLCT-BIO-08-54, there were altogether 3 major bleeds experienced by 2 of the 8 subjects and 2 joint bleeds in one subject.
The MAH suggests that the higher number of bleeds per patient in children <12 years old may be due to the generally high variability in bleeding tendency among VWD patients (e.g., some patients are more prone to oral mucosal bleedings than others), but also due to the higher activity in children, which may result in more injuries, compared with adults; 20.9% of bleeding events in Arm 1 of study CSLCT-BIO-08-52 were trauma-induced compared with none in the Arm 3 of study CSLCT-BIO-08-54.

Haemostatic Efficacy in Non-surgical Bleeding Events occurring during prophylaxis

In study paediatric CSLCT-BIO-08-52, 73 of the 91 events and in study CSLCT-BIO-08-54, all 10 bleeds were treated with human coagulation FVIII/VWF complex.

In both studies, the haemostatic efficacy of human coagulation FVIII/VWF complex per bleeding event was assessed as either excellent (90.9% of bleeds in study CSLCT-BIO-08-54 and 80.8% in study CSLCT-BIO-08-52) or good. (Table 21). Haemostatic efficacy in the treatment of bleeds occurring during prophylaxis was thus globally equivalent in the paediatric and adult subjects,

In supportive study CSLCT-BIO-03-97, the 3 adult subjects receiving prophylaxis treatment reported overall a higher number of bleeds (22) than those in study CSLCT-BIO-08-54: 1 subject each with 1, 3, and 17 bleeding events, respectively, over a period of 12 months, and the 4th subject was a 3 year old with 1 minor bleeding event over a period of 6 months. The investigator made a retrospective assessment of haemostatic efficacy in these patients at the three monthly follow-up visits and efficacy was on all occasions was considered to be good or excellent.

Table 25: Overview of number of bleeding events and of investigator's assessment of haemostatic efficacy per event (prophylaxis regimen)

	No. of NSB events	**Median (range)**	**No. of NSB events treated** [a]	**No. (%) of NSB events Excellent**	**No. (%) of NSB events Good**
CSLCT-BIO-08-54 (Arms 1 and 3) (N=9) [b]					
All NSB events	Arm 3:10 Arm 1: 10	Arm 3: 1.0 (1 to 6)	10 1	10 (90.9) -	1 (9.1) 1
Major [c]			4	3 (75.0)	1 (25.0)
Minor			7	7 (100.0)	0
Joint			2	2 (100.0)	0
Mucosal			9	8 (88.9)	1 (11.1)
Muscle			0	0	0
CSLCT-BIO-08-52 (Arm 1) (N=4) [d]					
All NSB events	91	23.5 (9 to 35)	73	59 (80.8)	14 (19.2)
Major [c]			3	1 (33.3)	2 (66.7)
Minor			70	58 (82.9)	12 (17.1)
Joint			3	0	3 (100.0)
Mucosal			62	53 (85.5)	9 (14.5)
Muscle			0	0	0
Other			8	6 (75.0)	2 (25.0)

On-demand regimen

Haemostatic Efficacy during the on-demand regimen

Overall, the majority of events in the pivotal studies were assessed with either excellent or good haemostatic efficacy: 98.3% in study CSLCT-BIO-08-54, 100% in paediatric study CSLCT-BIO-08-52. This was also the case in study CSLCT-BIO-03-97 where there were only 4 bleeds in 6 subjects. In the Howman study in 43 paediatric subjects aged 5 months to 17.5 years there were 72 bleeds, with an assessment of excellent in approximately 80% good in approximately 18% and moderate in the rest.

Table 26. Investigator's assessment of haemostatic efficacy per bleeding event (on-demand regimen)

		Number (%) of NSB events			
	No. of NSB events [a]	**Excellent**	**Good**	**Moderate**	**None**
CSLCT-BIO-08-54 (Arm 2) (N=20) [b]					
All NSB events	407	375 (92.1)	25 (6.1)	7 (1.7)	0
Major [c]	125	117 (93.6)	2 (1.6)	6 (4.8)	0
Minor	282	258 (91.5)	23 (8.2)	1 (0.4)	0
Joint [d]	101	99 (98.0)	2 (2.0)	0	0
Mucosal [d]	291	261 (89.7)	23 (7.9)	7 (2.4)	0
Muscle	17	17 (100)	0	0	0
CSLCT-BIO-08-52 (Arm 2) (N=12) [e]					
All NSB events	80	36 (45.0)	44 (55.0)	0	0
Major [f]	26	13 (50.0)	13 (50.0)	0	0
Minor	54	23 (42.6)	31 (57.4)	0	0
Joint	11	2 (18.2)	9 (81.8)	0	0
Mucosal	65	30 (46.2)	35 (53.8)	0	0
Muscle	1	1 (100.0)	0	0	0
Other	3	3 (100.0)	0	0	0

Clinical studies in special populations

In the prophylaxis arms (Arm 3 and Arm 1) of Study CSLCT-BIO-08-54, all 8 patients were older than 18 years of age, mean 43.0 (s.d, 15.9) years, median 42.5 (range 21 to 68 years).

Study CSLCT-BIO-08-52 was specifically performed in children < 12 years old.

There were no further studies or data in special populations relevant to this procedure.

Supportive studies

Supportive data relevant to this procedure was available from studies CSLCT-BIO-03-97 and the Howman study - Howman et al (2011). The Shortt study (2007) was an investigator led study which retrospectively assessed the efficacy and safety of Voncento in VWD patients undergoing invasive procedures or surgery.

CSLCT-BIO-03-97

All but one of the 23 subjects in study CSLCT-BIO-03-97 were adults and the study provided principally efficacy and safety data on the use of Voncento in surgery with some data on non-surgical bleeding events and data on routine prophylaxis in 4 subjects.

The dosage guideline for prophylaxis was 20 - 50 IU/kg 2 to 3 times per week. All four prophylactic patients had at least one episode of spontaneous bleeding such as epistaxis or bleeding into joints (elbow, shoulder and ankle). Patient 06-A353 was known to play contact sport during the study and had 17 single episodes of bleeding either due to trauma (four events) or spontaneous bleeding. The four patients' diary cards were reviewed every 3 months, and at each of these follow-up visits the investigator made a retrospective

assessment of haemostatic efficacy. On all occasions, haemostatic efficacy was considered by the investigator to be Good or Excellent.

The three adult patients received prophylaxis for 12 months.
The 3-year-old boy (Subject 10A354) included in study CSLCT-BIO-03-97 was the only paediatric subject in the study and he was on prophylaxis treatment, which he received for >5 months. He experienced 1 minor bleeding event at the left ankle that did not require any corrective therapy.

Howman study

The investigator-led study reported by Howman et al (2011) retrospectively assessed the efficacy and safety of human coagulation FVIII/VWF complex in children and adolescents with VWD treated for surgery, NSB events, or continuous prophylaxis from April 2003 to February 2008.

The study included 25 males and 18 females paediatric patients with a median age of 10 years amd a range of 5 months to 17.5 years. Type 1 VWD was diagnosed in 21 subjects, while 4 subjects had Type 2A VWD, 6 had Type 2B VWD, 4 had Type 2M VWD, 1 had Type 2N VWD, and 7 subjects had Type 3 VWD.

The mean daily dose was 51 IU FVIII/kg (range: 13-151 IU FVIII/kg) for major surgery with a median treatment duration of 7 days (range: 1-24 days) and 45 IU FVIII/kg (range: 14-76 IU FVIII/kg) for minor surgery with a median treatment duration of 3 days (range: 1-8 days). For NSB events, the mean daily dose was 45 IU FVIII/kg (range: 16-192 IU FVIII/kg) with a median treatment duration of 1 day (range: 1-13 days).

Forty-two surgical events were treated: 10 major events in 10 subjects and 32 minor surgical events in 21 subjects. Four episodes of post-surgical bleeding events were also treated in 4 subjects, who had not received human coagulation FVIII/VWF complex to prevent bleeding during the procedure. A total of 72 NSB events were treated: 46 mucocutaneous in 11 subjects and 26 musculoskeletal or soft tissue bleedings in 13 subjects. Only tranexamic acid was used as an adjunctive therapy in these subjects.

The haemostatic efficacy for all surgical events was excellent or good in approximately 90% of events (90% major and 91% of minor surgical events). Haemostatic efficacy for all NSB events was rated as excellent or good in 94% of events, and within Type 3 VWD subjects in 98% of NSB events.

The blood loss during surgical events was assessed by the surgeon for 15 minor and 5 major surgical events and in all cases was considered to be less than or equivalent to that normally expected in subjects without a bleeding disorder.

Two subjects with Type 3 VWD received long term prophylaxis with human coagulation FVIII/VWF complex to prevent bleeding. One subject had started prophylaxis therapy at 9 months of age which was successful at preventing recurrent epistaxis. However, a second subject suffered ongoing ankle joint bleeding, and was reported as having a low responding inhibitor, after 4 years of prophylaxis.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The general design, endpoints and sample size of both studies *CSLCT-BIO-08-54* (Routine prophylaxis in subjects ≥ 12 years old) and *CSLCT-BIO-08-52* (efficacy and safety in paediatric patients < 12 years old) are in line with the Guideline on the Clinical Investigation of Human Plasma Derived von Willebrand Factor Products (CPMP/BPWG/220/02).

All patients who received routine prophylaxis in Arm 3 of study CSLCT-BIO-08-54 were > 18 years old, thus the study did not contribute data on routine prophylaxis in adolescents. Notably, 6 of the 8 subjects in Arm 3 had Type 3 VWD, a severe disease type with negligible levels of VWF thus comprising patients most likely to need or to benefit from routine prophylaxis.

In study CSLCT-BIO-08-52, 10 of the 17 subjects had Type 3 VWD, which can be considered a relatively large number of children to include with this rare disease.

The dosage ranges proposed in the schedule to be followed during both studies are somewhat lower than that of 40 to 80 IU/kg vWF:RCo and 20 to 40 IU/kg FVIII:C recommended in the Guideline on the Core SmPC for Human Plasma Derived von Willebrand Factor, for achieving haemostasis.

The target FVIII/vWF levels are close to that recommended (> 60% vWF:RiCo and > 40% FVIII:C) in the Core SmPC which proposes only a very global target level, and not specified for example for haemostasis in bleeds or in major or minor surgery. However, the Core SmPC gives no dosage recommendation for routine prophylaxis and no specific dosage recommendations for the paediatric population but states that where indicated in children information should be provided on whether dose and frequency of administration differs to that in adults.

Overall, the dosage guideline used in both studies can be considered acceptable for the purposes of study CSLCT-BIO-08-54 but in view of the doses used in the paediatric study of Howman et al (2010), it might be considered to be somewhat low for paediatric study CSLCT-BIO-08-52.

Efficacy data and additional analyses

Efficacy in preventing bleeds during routine Prophylaxis

Patients ≥12 years

Routine prophylaxis in adult subjects in study CSLCT-BIO-08-54 was clearly shown to be efficacious in preventing spontaneous bleeding events as the mean (2.0, s.d 2.2) and median (1.0, range 1 to 6) number of bleeding events over 12 months was much lower in the 8 subjects who continued on to receive routine prophylaxis in Arm 3 compared to the mean of 26.7 (SD 24.2) and median of 19.5, range 2 to 82 in the 20 subjects on on-demand treatment in Arm 2.

Importantly, during prophylaxis, there were 3 major bleeds in 2 subjects and 1 subject experienced 2 joint bleeds. In comparison, in the same 8 subjects during on-demand treatment, 5 subjects experienced a median of 7.0 major bleeds (range 2 to 59) and 3 subjects experienced a median of 34 joint bleeds (range 7 to 58).

Furthermore, efficacy in the treatment of all the 10 reported bleeds in subjects on prophylaxis was reported as excellent. Thus routine prophylaxis was successful in these subjects.

No data on routine prophylaxis was obtained in adolescents, which is not considered to be of concern.

Paediatric patients <12 years

In the 4 paediatric patients (age < 12 years) on routine prophylaxis, the efficacy of the prophylaxis in preventing bleeds was apparently less than in the 12 months prior to study entry. As suggested by the MAH in the CSR of study CSLCT-BIO-08-52, this difference in the number of bleeds might be attributable to underreporting during the prior non-study period of 12 months compared to the stringent reporting during the study period because of the use of a diary and intensive follow-up by the investigator.

The median number of major bleeds per subject in the prophylaxis arm was half that in the on-demand arm and the median number of joint bleeds was similar. However it is difficult to draw conclusions with such small numbers and the populations in the 2 arms were not similar. In prophylaxis Arm 1, three of the 4 subjects had the most severe type of VWD, Type 3 and one subject had Type 2A whereas in on-demand Arm 2, approximately half of the subjects had Type 3 VWD (7/13) and the other 6 had Type 2A.

The number of bleeds per subject was higher in the on-demand arm compared to the prophylaxis arm. However the number of subjects was much smaller in the prophylaxis arm and there was no comparison between on-demand treatment and prophylaxis in the same subjects, which hampers interpretation of the numbers of bleeds. It is of some significance that approximately 97% of all bleeds in the prophylaxis arm were rated as minor compared to 73% in the on-demand arm.

It is also of note that for 2 of the subjects on prophylaxis during study CSLCT-BIO-08-52, no treatment was required for approximately one third of their minor bleeds and for one subject 9% of the minor bleeds did not need treatment. Overall, a higher percentage of bleeds did not require treatment within patients on prophylaxis compared to patients receiving only on-demand treatment (16.7% of bleeds).

Efficacy in the treatment of bleeding events

The paediatric data in children < 12 years from study CSLCT-BIO-08-52 show a high level of haemostatic efficacy (efficacy reported as excellent in approximately 80% of bleeds) in the treatment of spontaneous and traumatic bleeding events in the 4 subjects on prophylaxis. However, the level of haemostatic efficacy reported was lower in the 12 subjects receiving only on-demand treatment with efficacy reported as excellent in only 45% of bleeds.

Although a clinically relevant degree of haemostatic efficacy was reached in the on-demand treatment of bleeds in the paediatric subjects in study CSLCT-BIO-08-52, overall it was at a lower level than in the adult and adolescent subjects in study CSLCT-BIO-08-54. Haemostatic efficacy was rated as excellent in approximately half of the bleeds and good in the rest compared to 90% excellent in the adult and adolescent subjects.

It is reassuring that efficacy was rated as excellent for the majority (9 of 13) of the major mucosal bleeds during on-demand treatment in the paediatric patients as these are known to be difficult to treat. On the other hand, in the case of joint bleeds haemostatic efficacy was rated as good for 9 of 11 bleeds and for 2 bleeds it was rated as excellent.

Dosing

Prophylactic dose in patients ≥12 years

In study CSLCT-BIO-08-54, the mean (±s.d.) average dose per infusion given for prophylaxis was 28.8 (± 4.1) and the median average dose was 28.1 (range 25 to 35) IU VWF:RCo/kg, according to protocol to be given one to 3 times weekly. These doses were effective in reducing the number of bleeds and in reducing the number of major bleeds in the 8 subjects who first were treated on-demand in Arm2 and then received a prophylactic regimen in Arm 3. The median number of infusions per month in Arm 3 varied between 4.0 and 7.0. These doses and dose frequencies are considered to support the prophylactic regimen of 25 – 40 IU/kg VWF:RCo/kg 1 to 3 times per week recommended by the MAH in patients ≥12 years. This is included in the SmPC section 4.2.

Dosing in paediatric patients <12 years

Dose for the treatment of bleeds

According to the protocol of paediatric study CSLCT-BIO-08-52, the initial dose for the treatment of bleeds was to be 25 - 50 IU/kg VWF:RiCo with the aim of reaching a target VWF peak level of >50% (FVIII level >30%). It seems possible that this dosage range recommended in the protocol may not have been optimal for all patients <12 years.

In the on-demand arm (n=12) of study CSLCT-BIO-08-52 in patients <12 years, the mean of the doses per patient actually used for the treatment of bleeding ranged from approximately 35 to 70 IU/kg VWF:RCo and the median of the doses per patient ranged from approximately 30 to 80 IU/kg VWF:RCo. Over all the 12 subjects, the average dose (± s.d.) was 47.6 (± 16.8) IU/kg VWF:RCo and the median dose was 40.8 (range 30.2 to 88.6) IU/kg VWF:RCo (Table 8 of the Applicant's response to this question).

For comparison, in pivotal study CSLCT-BIO-08-54 in patients aged ≥12 years, the 20 subjects in the on-demand arm (Arm 2) received a mean (± s.d.) average dose per infusion of 37.8 (± 8.7) IU/kg VWF:RCo and the median average dose per infusion was 36.1 IU/kg (range: 29 to 64) IU/kg VWF:RCo (Table 19 of this report: Summary of efficacy for Study CSLCT-BIO-08-54).
Thus for children <12 years the mean and median doses per infusion used for the treatment of bleeds were higher than in patients ≥12 years. The doses used by children <12 years fell within the proposed on-demand dosing range of 40 - 80 IU/kg VWF:RCo but reached a higher level within this range than the doses used in patients ≥12 years. (See also discussion on Clinical pharmacology).

Therefore the dosing regimen for the treatment of bleeding in the *Paediatric VWD population* was agreed as: "Usually 40 - 80 IU/kg of von Willebrand factor (VWF:RCo) corresponding to 20 - 40 IU FVIII:C/kg of body weight (BW) are recommended in paediatric patients to treat a bleed. " in section 4.2 of the SmPC.

Prophylactic dose in patients <12 years

Further analysis in the MAH response to the RfSI reveals that in paediatric study CSLCT-BIO-08-52, the median average dose per infusion during the period on prophylaxis was 62.6 IU VWF:RCo/kg. There was a large total number of infusions in Arm 1, including infusions given for prophylaxis and for the treatment of bleeding events. The MAH has confirmed that the mean and median prophylactic doses used in these children were approximately 60 IU/kg and that the frequency of administration ranged from 1 to 3 times a week.

At a single patient level, in the 3 subjects who had been on a prophylactic regimen prior to entry to study CSLCT-BIO-08-52, the number of bleeding events per individual during the 12 months on was rather similar in 2 subjects (from 28 to 34 in subject 110101 and from 19 to 14 in subject 110102) and higher in one subject (from 9 to 35 in subject 110103) than in the 12 months prior to study entry.
The prophylactic doses used per individual were similar in the subjects on prophylaxis before and during the study and were also used by these patients in the continuation Study CSLCT-BIO-06-94. As discussed in the clinical pharmacology section, the dosing recommendation in section 4.2 of the SmPC for prophylaxis for patients aged <12 years old: Based on results from a clinical trial in which paediatric patients under 12 years of age were shown to have lower exposure of VWF, a prophylactic dose range of 40 – 80 IU VWF:RCo/kg body weight 1 to 3 times a week should be considered. (see Section 5.2).
The dose and duration of treatment will depend on the clinical status of the patient, as well as their VWF:RCo and FVIII:C plasma levels.

2.4.3. Conclusions on the clinical efficacy

The data from Study CSLCT-Bio-08-54 support an indication in routine prophylaxis to prevent spontaneous and traumatic bleeding events in the adult population with a recommended prophylactic dose of 25 - 50 IU/kg VWF:RCo 1 to 3 times per week.

The data from Study CSLCT-BIO-08-52 support use in paediatric patients <12 years old. For the treatment of bleeds, it is agreed that the dose range of 40 - 80 IU/kg VWF:RiCo, the same as for patients ≥12 years, can be considered appropriate. Efficacy in routine prophylaxis has also been shown in 4 patients <12 years old with severe VWD.
The protocol of the Post-Marketing Study CSLCT-BIO-12-83, which was agreed as part of the post authorisation measures in the initial approval of Voncento, was amended to incorporate the dose range 40-80 IU VWF:RCo/kg body weight for prophylaxis treatment in children.

2.5. Clinical safety

Introduction

The safety of human coagulation FVIII/VWF complex has been established in clinical studies for the treatment of both haemophilia A and VWD, and is supported by post-marketing surveillance data.

Key issues with regard to safety of FVIII concentrates are inhibitor development, the potential for viral contamination, and in patients with VWD the risk of VTE due to elevated FVIII levels. As with any intravenous protein product, allergic type hypersensitivity reactions are possible and symptoms indicative of such reactions are an identified risk for Human coagulation FVIII/VWF complex. Whereas inhibitor development is no less a concern than in previous decades, the problems of virus contamination in plasma derived products have been largely resolved with successive improvements in the manufacturing process required by regulatory guidelines. Episodes of venous VTE have been reported in the literature in subjects with VWD receiving VWF/FVIII replacement therapy, especially in the setting of known risk factors for thrombosis (Mannucci PM et al, 2002; Makris M et al, 2002).

Nevertheless, the number of such events in the literature has remained very low.

Table 27. Studies providing safety data for Von Willebrand Disease.

Study identifier (Location)	Clinical phase Study dates	No. of centres Countries	Study design	Primary objective(s)	Study product(s) Dose regimen	No. of subjects Sex Mean age ±SD (range)	Safety endpoints
Pivotal safety and efficacy studies in VWD							
CSLCT-BIO-08-54 (Section 5.3.5.2.2 [VWD])	II/III June 2009 - February 2012	6 Brazil, Bulgaria, Poland, Russia, and Ukraine	Open-label multi-centre study	To investigate the initial and repeat PK profile of Biostate in subjects with severe VWD. To assess the haemostatic efficacy of Biostate in subjects with VWD who require a VWF product to control an NSB event. To assess the effectiveness of a prophylaxis regime as compared to on-demand therapy with Biostate in preventing NSB events.	Human coagulation FVIII/VWF complex PK component: 80 IU/kg VWF:RCo each for initial and repeat PK. Efficacy component: As required according to the subject's baseline FVIII:C and/or VWF:RCo levels.	22 (Type 1: 5, Type 2A: 4, Type 3: 13) 10 males, 12 females 33.6 ± 15.2 years (15-68 years), including 3 adolescents aged 15-16 years	Evaluation of AEs, biochemistry, haematology, FVIII and VWF inhibitors, physical examination, and vital signs.
CSLCT-BIO-08-52 (Section 5.3.5.2.6 [VWD])	III July 2010 - August 2013	8 Georgia, Germany, Guatemala, Lebanon, Belarus, and Ukraine	Open-label, multi-centre study	To assess the efficacy of Biostate in paediatric subjects with VWD. To investigate the PK profile of Biostate in paediatric subjects with VWD.	Human coagulation FVIII/VWF complex PK component: 80 IU/kg VWF:RCo each for initial and repeat PK. Efficacy component: As required according to subject's baseline VWF:RCo levels.	17 (Type 2A: 7, Type 3: 10) 7 males, 10 females 5.2 ± 3.4 years (0-11 years), including 9 subjects aged <6 years	Evaluation of AEs, biochemistry, haematology, FVIII and VWF inhibitors, physical examination, and vital signs.
Supportive safety and efficacy studies in VWD							
CSLCT-	I	5	Single-blind,	To evaluate the PK of Biostate and	Biostate RP	12 (Type 1: 4;	Evaluation of

Study identifier (Location)	Clinical phase Study dates	No. of centres Countries	Study design	Primary objective(s)	Study product(s) Dose regimen	No. of subjects Sex Mean age ±SD (range)	Safety endpoints
BIO-00-75 (Section 5.3.3.2.3)	January - May 2003	Australia	randomised, cross-over, multi-centre	AHF (HP) in subjects with VWD, in order to determine comparability.	Single infusion of 60 IU VWF:RCo/kg (corresponding to 30 IU FVIII/kg).	Type 2B: 2; Type 2M: 1, Type 3: 5) 8 males, 4 females 38 ± 11.9 years (19-58 years)	AEs, biochemistry, haematology, and vital signs.
CSLCT-BIO-03-97 (Section 5.3.5.2.3 [VWD])	II/III December 2004 - May 2007	8 Australia New Zealand	Open-label, multi-centre	To evaluate the efficacy and safety of Biostate in the treatment of NSBs, in the management of surgical procedures and prophylactic therapy in subjects with VWD where DDAVP treatment was ineffective, inadequate, or contraindicated.	Biostate RP As required, dependent on the subject's baseline FVIII:C and/or VWF:RCo levels.	23 (Type 1: 7; Type 2A: 2; Type 2M: 6; Type 3: 7; unknown: 1) 12 males, 11 female 47.2 ± 20.9 years (3-85 years), incl. 1 child aged 3 years.	Evaluation of AEs, biochemistry, haematology, FVIII inhibitors, and physical examination.
Shortt study (Section 5.3.5.2.4 [VWD])	N/A April 2003 - September 2005	3 Australia	Retro-spective	To evaluate the safety and efficacy of Biostate use in the prevention of bleeding in VWD subjects undergoing invasive or surgical procedures.	Biostate RP Prophylactic treatment for invasive or surgical procedures.	43 (Type 1: 26; Type 2A: 8; Type 2B: 4; Type 3: 5) 21 male, 22 female 52 years (19-80 years)	Evaluation of AEs potentially attributable to the IMP, routine haematology, where available.

Patient exposure

In the prospective clinical studies, 74 subjects with VWD, including 3 adolescent subjects (all in study CSLCT-BIO-08-54) and 18 paediatrics below 12 years of age (17 subjects in study CSLCT-BIO-08-52 and 1 in study CSLCT-BIO-03-97) were exposed to human coagulation FVIII/VWF complex as shown in Table 28. Investigator-led studies included 43 adult VWD subjects (Shortt study) and 43 paediatric subjects (Howman study).

Table 28. Patient exposure in VWD

	Patients exposed**			Patients exposed to the proposed dose range			Patients with long term* safety data	
	Adult and adolescent 12 – 18 yrs		Paed. <12 yrs	Adult and adolescent 12 – 18 yrs		Paed. <12 yrs	Adult and adolescent 12 – 18 yrs	Paed. <12 yrs
Open studies	Adult	Adlsc		Adult	Adlsc			
CSLCT-BIO-08-54	19	3		19	3		12 months: 22	
CSLCT-BIO-08-52			17 of whom 9 were <6years			17 of whom 9 were <6years	24 months: 8 adults (one subject stopped prophylaxis after 10.5 months thus total < 24 mo)	12 months: 17 of whom 9 were <6years
CSLCT-BIO-03-97	22		1			1	17	6 months:1 in 03-97
CSLCT-BIO-00-75	12							
Total	53	3	18				12 months: 39	12 months: 13
post marketing Studies with Voncento								
Shortt study (surgery)	43 adults							
Howman study	43 paediatric patients aged 0.4 to 17 years							2

* In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

**The retrospective Howman study *(Haemophilia 2011)* included 43 paediatric patients aged 0.4 to 17 years but apart from 2 paediatric subjects on routine prophylaxis, results were for the most part not reported according to age subgroups.

Adults

Study CSLCT-BIO-08-54:

All subjects completed at least 12 months of treatment.

On-demand treatment: Subjects in the on-demand arm (Arm 2) had a median number of 20.0 infusions (range: 3-92) over 12 months at a median IMP dose of 36.1 IU VWF:RCo/kg (range: 29 64 IU/kg).

Prophylaxis treatment: All subjects received prophylaxis therapy for 12 months with a median number of 72.5 infusions (range: 16-118), with the exception of the single subject in Arm 1 who received 197 infusions over 15 months and 1 subject in Arm 3 who withdrew consent after about 10.5 months of prophylaxis treatment.

Paediatric patients

Study CSLCT-BIO-08-52 (patients below 12 years of age)

All 17 paediatric subjects completed the 12 month treatment period of the study.
Prophylaxis treatment: The 4 subjects of the prophylaxis treatment arm (Arm 1) of study CSLCT-BIO-08-52, received a median number of 137.5 infusions. In Arm 1, a median number of 119 infusions (range: 45-161) were administered as prophylaxis, and a median of 17 (8-41) to treat a bleeding event.
On-demand treatment: The 13 subjects in the on-demand arm (Arm 2), had a median number of 8.0 infusions (range 1-53) at a median dose of 50.9 IU VWF:RCo/kg per infusion (range: 35.4-115.1 IU VWF:RCo/kg).

The 3-year-old boy in VWD study CSLCT-BIO-03-97 received 66 infusions of 500 IU FVIII each (about 29 IU FVIII/kg body weight *(Assessor: corresponding approximately to 60 IU VWF:RCo/kg))* as prophylaxis treatment.

Supportive retrospective investigator-led studies in VWD

Shortt study (2007, principally surgery and 1 child on prophylaxis): The average daily dose of human coagulation FVIII/VWF complex was 29 IU FVIII/kg (range: 9-65 IU FVIII/kg). The mean duration of treatment for each event was 4 days (range 1-13 days).

Howman study paediatric study (principally surgery and 2 subjects on prophylaxis): The median duration of treatment for major surgeries was 7 days (range: 1-24 days) at a mean daily dose of 51 IU FVIII/kg (range: 13-151 IU FVIII/kg). Minor surgeries were treated for a median duration of 3 days (range: 1-8 days) at a mean dose of 45 IU FVIII/kg (range: 14 76 IU FVIII/kg). For NSB events, the median duration was 1 day (range: 1 13 days) and the mean dose 45 IU FVIII/kg (range: 16-192 IU FVIII/kg).

Long term exposure
With regard to long term exposure, in the prospective clinical studies, it seems that 39 VWD patients ≥12 years (*Assessor's calculation)*, and 13 paediatric patients under 12 years have been exposed to human coagulation FVIII/VWF complex for up to 12 months, intermittently at varying frequencies for the treatment of non-surgical and surgical bleeding events.
Eight adults who continued from on-demand treatment in Arm 2 of study CSTCT-BIO-08-54 on to routine prophylaxis in Arm 3 of that study receiving doses 1 to 3 times weekly and reached an exposure of (in one case almost) 24 months.

Overall the exposure in 10 adults (studies CSLCT-BIO-08-54 and CSLT-BIO-03-97) and 5 subjects < 12 years (studies CSLCT-BIO-08-52 and CSLT-BIO-03-97) during long term routine prophylaxis is considered adequate to assess the safety of the treatment regimen which only a subset of subjects with severe VWD are likely to need.
Also, the exposure overall in 18 paediatric subjects < 12 years is considered adequate for assessing the safety and it can be taken into consideration that a post-marketing study will follow.

Adverse events

Adults and paediatric patients

A total of 508 treatment-emergent adverse events (TEAEs, ie, with onset after first dose of study medication) were reported during the clinical studies, 210 in haemophilia A studies (143 in pivotal study CSLCT-BIO-07-47, 2 and 65 in supportive studies CSLCT-BIO-95-30 and CSLCT-BIO-95-41, respectively) and 298 in VWD studies (86 and 77 in pivotal studies CSLCT-BIO-08-54 and CSLCT-BIO-08-52, respectively, and 24 and 111 in supportive studies CSLCT-BIO-00-75 and CSLCT-BIO-03-97, respectively). An overview of the number of subjects experiencing at least 1 TEAE during the prospective clinical studies is provided by AE type and study in Table 29.

Table 29: Overview of the number of subjects experiencing at least 1 TEAE during the prospective clinical studies.

Type of adverse event	Number (%) of subjects / Number of TEAEs						
	Studies in haemophilia A subjects			Studies in VWD subjects			
	CSLCT-BIO-07-47 (N=81)	CSLCT-BIO-95-30 (N=16)	CSLCT-BIO-95-41 (N=30)	CSLCT-BIO-08-54 (N=22)	CSLCT-BIO-08-52 (N=17)	CSLCT-BIO-00-75 (N=12)	CSLCT-BIO (N=23)
Any TEAEs	39 (48.1) / 143	1 (6.3) / 2	21 (70.0) / 65	15 (68.2) / 86	12 (70.6) / 77	10 (83.3) / 24	22 (95.7)
Possibly related TEAEs	8 (9.9) / 18	1 (6.3) / 2	6 (20.0) / 23	2 (9.1) / 2	2 (11.8) / 2	2 (16.7) / 5	2 (8.7) / 2
SAEs	4 (4.9) / 6	0	1 (3.3) / 1	1 (4.5) / 3	0	1 (8.3) / 1	2 (8.7) / 2
Possibly related SAEs	0	0	0	0	0	0	0
AEs leading to permanent treatment discontinuation	1 (1.2) / 2	0	1 (3.3) / 6	0	0	0	0
Possibly related TEAEs leading to permanent treatment discontinuation	0	0	1 (3.3) / 6	0	0	0	0
Death	0	0	0	0	0	0	0

AE = adverse event; N = number of subjects; SAE = serious adverse event; TEAE = treatment-emergent adverse event; VWD = Von Willebrand dise

Source: Section 5.3.5.2.2 (haemophilia A), CSLCT-BIO-07-47, Table 23; Section 5.3.3.2.2, CSLCT-BIO-95-30, Section 12.4; Section 5.3.5.2.3 (haem A), CSLCT-BIO-95-41, Sections 13.4.4 and 13.4.5, Table 7.1, Listings 20.1 and 20.2; Section 5.3.5.2.2 (VWD), CSLCT-BIO-08-54, Table 14.3 Section 5.3.5.2.6 (VWD), CSLCT-BIO-08-52, Table 27; Section 5.3.3.2.3, CSLCT-BIO-00-75, Listings 11.1 and 11.2; Section 5.3.5.2.3 (CSLCT-BIO-03-97, Sections 12.2.1 and 12.2.3, Listing 16.2.10; Section 2.7.4.7.1.

Serious adverse events

Adults and paediatric patients

A total of 9 subjects experienced serious adverse events (SAEs) during the clinical studies, 5 subjects with haemophilia A and 4 subjects with VWD.
None of these SAEs were considered by the investigator to be possibly, probably, or definitely related to human coagulation FVIII/VWF complex or to study procedures which can be agreed based on the data submitted.

Serious adverse event / deaths / other significant events

No deaths occurred during or shortly after any of the clinical studies in either the haemophilia A or VWD subject populations.

Significant adverse events

- No positive FVIII or VWF inhibitor titres occurred during any of the prospective clinical studies.
Please see "Immunological Events" below.
- No VTE (venous thromboembolism) events were reported in any of the studies.
- No indication of human coagulation FVIII/VWF complex causing allergic or anaphylactic reactions was seen in clinical studies.
- During the studies that provided safety data, no cases of suspected transmission of hepatitis virus or parvovirus B19 occurred.

The population studied is very small with regard to the likelihood of detecting uncommon events. Nevertheless it can be concluded that the adverse event profile is very benign.

No safety concern specific to the paediatric population has been identified.

Overdose
It is noted that 3 subjects in the PK part of paediatric study CSLCT-BIO-08-52 received doses which were a factor 2 too high. This also occurred in one case in pivotal VWD study CSLCT BIO 08 54 in adults and adolescents. These reports were not associated with any TEAEs.
These were apparently due to incorrect dosing because of confusion arising from the labelling both in units of FVIII and in units of VWF (the number of units of FVIII in the product is half that of VWF). The subjects were dosed according to the labelled FVIII:C content and not the VWF:RCo content.
This remains a point of concern and will be retained in the RMP.

Laboratory findings

Adults and paediatric patients

Overall, there were no consistent changes in mean haematology or clinical chemistry values across the studies, and no trends were observed in changes in individual haematology or clinical chemistry values. Also, no consistent statistically or clinically significant changes from pre-dose values were noted in vital signs in any of the clinical studies.

Safety in special populations

No apparent differences between the safety of human coagulation FVIII/VWF complex in adolescents (n=8: 5 subjects with haemophilia A and 3 with VWD) and that in adults were seen.

Pivotal study CSLCT-BIO-08-52 assessed the safety of human coagulation FVIII/VWF complex in paediatric subjects <12 years of age. Apart from a slightly different AE reporting profile, no clinically relevant differences were seen in safety findings between children and adults, which is supported by the available clinical experience in other studies (including the Howman study) and post-marketing information.

The safety of human coagulation FVIII/VWF complex in the geriatric population has not been systematically studied. However, subjects in the clinical trials have included individuals up to 85 years. Updated information on the adverse drug reactions (ADRs) experienced by elderly patients (≥ 65 years) is tabulated for clinical studies (CT) and post-marketing data (PM) has been supplied by the MAH in the response to the RfSI (Table 30).

Table 30. Number of ADRs reported by patients (PM) or subjects (CT), by age group

MedDRA Terms	Age <65 number		Age 65-74 number		Age 75-84 number		Age 85+ number	
	PM	CT	PM	CT	PM	CT	PM	CT
Total ADRs: 181 PMS*	168	57	13	0	0	0	0	0
Serious ADRs – Total	93	3	3	0	0	0	0	0
- Fatal	3		0	0	0	0	0	0
- Hospitalization/prolong existing hospitalization	11		3	0	0	0	0	0
- Life-threatening	28		0	0	0	0	0	0
- Disability/incapacity	5		0	0	0	0	0	0
- Other (medically significant)	81	3	1	0	0	0	0	0
ADR leading to drop-out	0		0	0	0	0	0	0
General disorders and administration site conditions		2						
Psychiatric disorders	2	3	0	0	0	0	0	0
Nervous system disorders	14	17	0	0	0	0	0	0
Accidents and injuries	6		0	0	0	0	0	0
Cardiac disorders	0	4	0	0	0	0	0	0
Vascular disorders	12		0	0	0	0	0	0
Cerebrovascular disorders	0		0	0	0	0	0	0
Infections and infestations	16		0	0	0	0	0	0
Anticholinergic syndrome	0		0	0	0	0	0	0
Quality of life decreased	0		0	0	0	0	0	0
Sum of postural hypotension (1), falls, black outs, syncope, dizziness (6), ataxia, fractures (1)	8		0	0	0	0	0	0
<other AE appearing more frequently in older patients>	N/A		N/A	0	0	0	0	0

*cut off date 12-Aug-2014

- No new ADRs were reported in Arm 3 of CSLCT-BIO-08-54,
- 2 AEs which were 'possibly related' were reported for paediatric subjects in study CSLCT-BIO-08-52 (erythema at infusion site and pyrexia, both non-serious, both resolved within 1 day; both General disorders and administration site conditions)

- No ADRs were reported in the extension study CSLCT-BIO-09-64; Subject 08-54-05001 aged 68 continued into the extension study, but reported no ADRs; no other adults in this study were ≥65 years of age.

In addition, in study CSLCT-BIO-10-67 (study terminated early) in haemophilia A (treatment for immune tolerance induction (ITI therapy)) 3 ADR were reported: hydrocephalus (Nervous system disorders, SAE), ischemic stroke (nervous system disorder, SAE), stenosis of the a carotis (Nervous system disorder, SAE).

The adverse events described in the single child in the terminated ITI study CSLCT-BIO-10-67 have been evaluated in a previous procedure (EMEA/H/C/002493/0000/P46). It was concluded that the patient had underlying pathology and that the B/R remained positive.

In patients aged 65 to 74 years, there were 13 ADRs of which three were serious, but no information is given on the nature of these adverse events.

Immunological Events

Inhibitors

No positive FVIII or VWF inhibitor titres occurred during any of the prospective clinical studies, with 1 exception: a positive FVIII inhibitor finding was reported for 1 subject at the final visit in study CSLCT-BIO-07-47; this case was also reported as an SAE (aggravation of pre-existing FVIII inhibitors) that led to study discontinuation. In supportive VWD study CSLCT-BIO-03-97, concerns were raised about a suspected inhibitor in 1 subject who had very low (zero) levels of VWF:RCo for 2 NSB events although adequate doses of human coagulation FVIII/VWF complex had been administered. However, VWF inhibitors were not measured in this study. In the retrospective investigator-led Howman study (Howman et al, 2011), 1 subject with Type 3 VWD was reported to have a low responding inhibitor that was noted after 4 years of prophylaxis treatment with human coagulation FVIII/VWF complex.

Allergic/Anaphylactic Reactions

During the clinical studies that provided safety data, no indication for human coagulation FVIII/VWF complex causing allergic or anaphylactic reactions was seen.

No allergic/anaphylactic reactions were observed in clinical studies but it is noted that In Table 6 of the Summary of Clinical safety a single case of upper airway obstruction is listed which occurred in one patient. In the context of other reported TEAEs it was considered not to represent a hypersensitivity reaction. The MAH has provided a narrative of this case explaining that the reported event was nasal obstruction with no elements suggestive of lower airway obstruction and that the event does not appear to have been due to a hypersensitivity reaction.

Safety related to drug-drug interactions and other interactions

No interactions between human coagulation FVIII/VWF complex and other medicinal products are known.

Discontinuation due to adverse events

In the studies supporting the current extension of indication of prophylaxis in VWD, and to include paediatric data in the SmPC, no discontinuations due to adverse events were reported.
Notably there were no discontinuations for any reason from the paediatric study CSLCT-BIO-08-52.

Post marketing experience

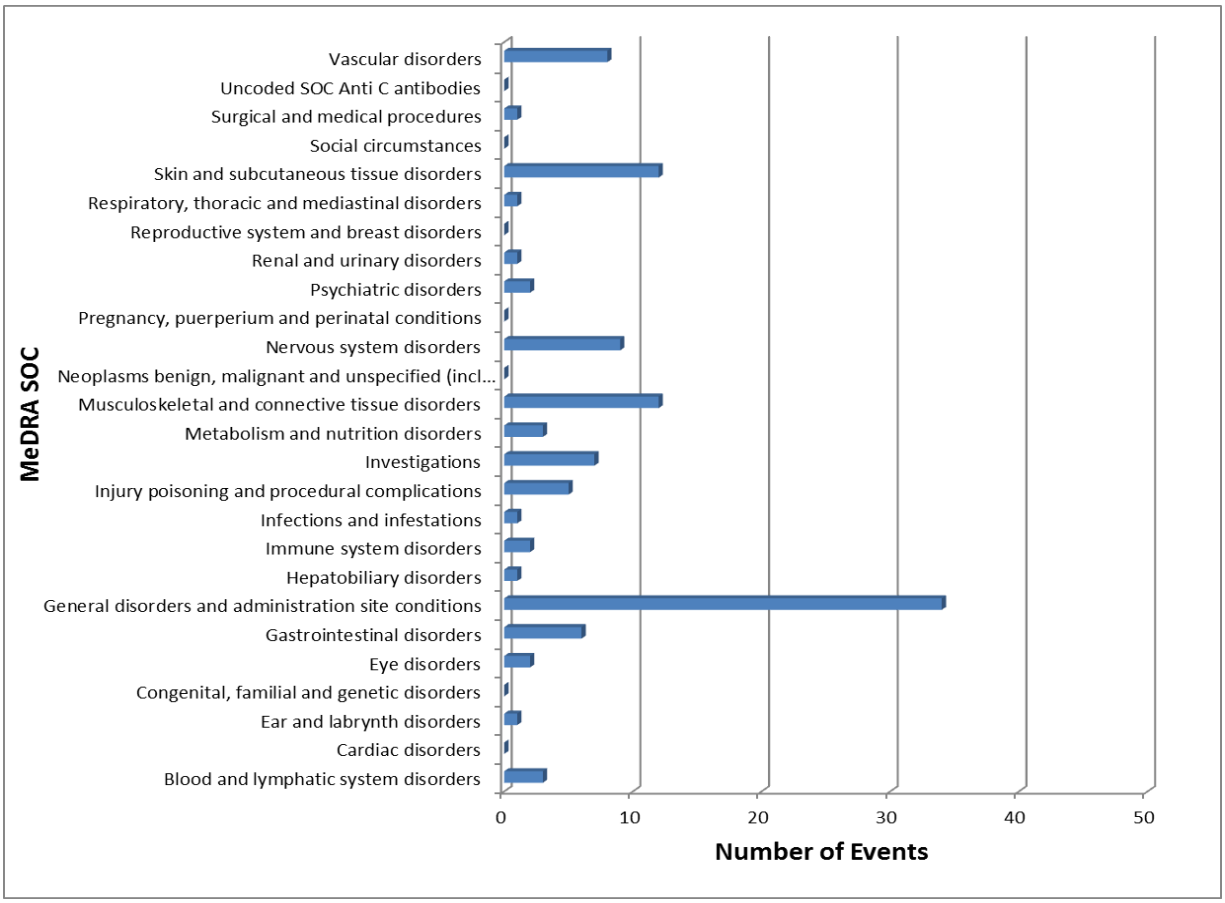
Voncento (human coagulation FVIII/VWF complex), is centrally authorised in the EU since 12 August 2013.

Post-marketing surveillance data collected by CSL comprise AE information collected in the company's database since first registration of human coagulation FVIII/VWF complex (Australia, August 2000). Post-marketing data were collected from a variety of sources including spontaneous reports (both consumer and health care professional), investigator-led studies (Shortt et al, 2007; Howman et al, 2011) and data from the Australian Adverse Drug Reactions Advisory Committee database.

Since launch of human coagulation FVIII/VWF complex and up to February 2014, 701,467,500 IU were distributed globally, and based on calculation from a single standard dose this total amount of human coagulation FVIII/VWF complex was administered (globally) in 350,734 single dose exposures, resulting in a total exposure of 2,248 patient years.

Since August 2000 up to 12 February 2014, 111 spontaneous ADRs from 39 case reports for human coagulation FVIII/VWF complex were reported by spontaneous data sources. The most frequently reported preferred terms were drug ineffectiveness (12), malaise (7), dizziness (6), nausea (5), and ecchymosis (5). Of the 111 ADRs, 38 were serious. No changes to the reference safety information were deemed necessary from the evaluation of these events. The cumulative experience to date of human coagulation FVIII/VWF complex is shown in Figure 3 below.

Figure 3. Post-marketing adverse events per MedDRA system organ class (cumulatively)



MedDRA = Medical Dictionary for Regulatory Activities; SOC = system organ class.

Adverse Events of Interest for FVIII/VWF Products

Viral transmission

No viral infections were reported in the studies supporting this application.

Hypersensitivity / anaphylactic reactions

Cumulatively, to date, there have been 12 reports of hypersensitivity and 1 report of anaphylactic reaction following the administration of human coagulation FVIII/VWF complex.

Inhibitor formation

Two cases of inhibitor formation (one in a subject with VWD and one in a subject with haemophilia A) to human coagulation FVIII/VWF complex were reported to CSL in 10 years of post-marketing surveillance.

Thromboembolic events

To date, there have been no post-marketing spontaneous reports of thromboembolic type events after treatment with human coagulation FVIII/VWF complex.

2.5.1. Discussion on clinical safety

Exposure

In the prospective pivotal clinical studies, close to 40 VWD patients ≥12 years and 13 patients < 12 years have been exposed to Voncento for up to 12 months, intermittently at varying frequencies for the treatment of non-surgical and surgical bleeding events.

In the pivotal studies CSLCT-BIO-08-54 and CSLCT-BIO-08-52 eight adults received an additional 12 months treatment (in one case 10.5 months) on a routine prophylaxis regimen reaching an exposure of 24 months and 4 additional paediatric patients <12years old were also treated for 12 months with a routine prophylaxis regimen. Altogether there were 9 subjects with Type 3 VWD of whom 6 were adults and 3 were children <12 years old with 2 <6 years old.

Although the numbers are not high, in view of the fact that only a subset of subjects with severe VWD are likely to need prophylaxis, overall the exposure in 10 adults and 5 subjects < 12 years in the prospective studies CSLCT-BIO-08-54, CSLCT-BIO-08-52 and CSLT-BIO-03-97 during long term routine prophylaxis is considered adequate to assess the safety of the treatment regimen.

Also, the exposure overall in 18 paediatric subjects < 12 years is considered sufficient to evaluate safety in that age group.
Three subjects aged from 12 to 18 years have been treated in the clinical studies but no subjects in this age range have been treated with a routine prophylaxis regimen. Given that there are data in children < 12 years and subjects from 19 years upwards, this is not considered to be a serious deficit.

Adverse Events

In the context of this procedure concerning patients with VWD, important potential risks are inhibitor development and the risk of VTE due to elevated FVIII levels. Also, as with any intravenous protein product, allergic type hypersensitivity reactions are possible particularly with repeated exposure. In plasma derived products there is also the potential for viral contamination.

During the studies that provided safety data, no cases of suspected transmission of hepatitis virus or parvovirus B19 occurred. No VTE (venous thromboembolism) events were reported in any of the studies.

There has been only one report of development of inhibitor to VWD which concerned a Type 3 VWD in the retrospective investigator led Howman study. The patient had developed a low responding inhibiting antibody to VWF after 4 years on a prophylactic regimen.

The MAH reports that no indication of human coagulation FVIII/VWF complex causing allergic or anaphylactic reactions was seen in clinical studies. However, as no narrative can be found, the MAH is asked to clarify the conclusion that, in the context of other reported TEAEs, a case of upper airway obstruction was considered not to represent a hypersensitivity reaction.

The data in the clinical studies submitted on the treatment of VWD did not reveal a particular pattern of AEs and the AEs reported most frequently post-marketing are to be expected due to the intravenous administration, to the bleeding disorder being treated or were non-specific.

Overall the adverse events reported in patients of all ages were mild and none led to discontinuation. There were no deaths during the clinical studies. Serious adverse events were reported during the clinical studies in 4 patients with VWD and none were considered by the investigator to be possibly, probably, or definitely related to human coagulation FVIII/VWF complex. The incidence and type of laboratory AEs do not raise concern and are not considered influencing the safety.

However, the numbers of patients with VWD in the clinical trials are small with regard to detecting uncommon adverse events and the safety profile in both VWD will be further evaluated in post-marketing study CSLCT-BIO-12-83 and will be followed in the PSURs.

There are few data in patients older than 65 years with VWD with one patient in this age range in the pivotal study CSLCT-BIO-08-54 who also received routine prophylaxis. Lack of data in this age range is included as missing information in the RMP.

The possibility of incorrect dosing due to product labelling in units of FVIII and VWF remained a real issue in the VWD studies submitted and should continue to be covered in the RMP. In the packaging and product information the MAH emphasises the dual content and different amounts of FVIII and VWF in the product in order to reduce the chance of dosage errors.

The favourable AE profile of Voncento as known in the post-marketing history is acknowledged, although it is considered that underreporting cannot be excluded.

The AEs reported most frequently post-marketing e.g. administration site conditions, skin and subcutaneous tissue disorders, musculoskeletal and connective tissue disorders, vascular disorders and nervous system disorders are to be expected due to the intravenous administration , to the bleeding disorder being treated or are non-specific.

Conclusions on clinical safety

From the data submitted, no unexpected adverse events or pattern of adverse events has emerged and the AEs reported were generally mild and not serious. No new safety concerns have arisen and the safety profile is considered to remain positive.

In particular, no significant issues of safety or ADRs were identified during treatment of a limited number (18) of paediatric patients ranging in age from <1 year to 11 years, including prophylaxis in 4 patients of whom 3 were <6 years.

Overall no safety concerns have arisen during routine prophylaxis regimens given to patients with severe VWD for a period of 12 months. The additional cases of overdose reported from clinical trials were included in section 4.9 but no adverse reactions have been associated with these reports (see SmPC). Risk of incorrect dosing was included in the RMP (See also RMP).

2.5.2. PSUR cycle

The PSUR cycle remains unchanged.

The next data lock point will be 18 August 2015.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 5.0 is acceptable. In addition, minor revisions were recommended to be taken into account with the next RMP update.

The clinical data provided in support of the variation application (CSLCT-BIO-08-52, CSLCT-BIO-08-54) showed that the safety profile of Voncento in paediatric patients was comparable to the established safety profile of the product; no new or unexpected risks were identified. The important potential risk 'Off-label use including in ITI therapy and children under 12 years' was narrowed to 'Off-label use including in ITI therapy'.

The proposal to remove the safety concerns 'Mild forms of haemophillia A' and 'Patients with AIDS and other chronic illnesses' from the missing information was supported as no specific safety concerns have been identified and neither foreseen with regard to use of Voncento in these populations.

The safety concern 'Immune Tolerance Induction Therapy' classified as missing information should be followed as important potential risk. Data on ITI in haemophilia A patients using a VIII product with a high VWF content would be of interest as there are few data on ITI with such a product.

The proposal to remove the safety concern 'Exposure date in non-Caucasian ethnic groups' was approvable as the MAH is requested to provide within the next PSUR (DLP: 12 August 2015), a detailed review of the current available data on the differences in inhibitor development between ethnic populations, and discuss the need to update the product information. Also, the MAH is requested to discuss the need for a RMP update, on the basis of the results of the data review.

Removing of missing information 'Paediatric data (< 12 years)' from the safety specification was approvable in view of the submitted data on use of Voncento in the paediatric VWD indication. The subsequently included mising information 'Off-label use in paediatric haemophilia A patients' should be changed to 'Use in paediatric haemophilia A patients'. The MAH commited to adapt the RMP accordingly in the upcoming variation.

No new pharmacovigilance activities have been proposed in this RMP update.

Finally, no changes to the risk minimisation measures have been proposed in this update.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.9, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, Annex II has been updated to amend the address of the manufacturing sites and the Labelling was updated with some editorial changes.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Routine prophylaxis treatment

Adults and adolescents: The median number of bleeding events during 12 months of routine prophylaxis in Study CSLCT-BIO-08-54 was reduced to 1.0 (range 1 to 6) compared to a median of 26.5 (range 18 to 82) in these patients during the previous 12 months. During prophylaxis in the adults, there were 3 major bleeds in 2 subjects and 1 subject experienced 2 joint bleeds, compared to 8 subjects during on-demand treatment, 5 subjects experienced a median of 7.0 major bleeds (range 2 to 59) and 3 subjects experienced a median of 34 joint bleeds (range 7 to 58). The single subject in Arm 1 of Study CSLCT-BIO-08-54 experienced 10 bleeds during 15 months of routine prophylaxis.

Concerning the on-demand treatment of bleeding events in the 12 paediatric patients <12 years of age in arm 2 of study CSLCT-BIO-08-52, haemostatic efficacy assessment of excellent or good as reported in about half the bleeds overall may be clinically acceptable but a higher rate of higher efficacy than reported in study CSLCT-BIO-08-52 might be clinically desirable. In this regard it is of importance that in these children haemostatic efficacy was rated as excellent in 9 of 13 major mucosal bleeds which are known to be difficult to treat

Children <12years:

Out of 4 paediatric subjects <12 years old, 3 of whom had Type 3 VWD, in study CSLCT-BIO-08-52 , in 2 of the 3 subjects on prophylaxis both prior to and during study CSLCT-BIO-08-52 the number of major bleeds was reduced compared to their previous prophylactic regimen and in one of these it remained the same. The single subject who had been on-demand treatment before going on to prophylaxis in study CSLCT-BIO-08-52 had one major bleed on prophylaxis compared to 2 in the prior 12 months of on-demand treatment.

Haemostatic efficacy in the treatment of bleeds occurring while on prophylaxis was reported as being excellent in all except one bleed in adults (a major mucosal bleed with efficacy rating of good in the single subject in Arm 1) and in the majority of bleeds in children < 12 years (efficacy rating of excellent in 80.8% of 73 bleeds and good in the rest).

Haemostatic efficacy in on-demand treatment

Adults and adolescents:
In study CSLCT-BIO-08-54 the investigator assessed haemostatic efficacy assessment in 407 events as excellent in 92.1%, good in 6.1% and moderate in 1.7%.

Major bleeding events: For the 125 major bleeds, the distribution of investigator efficacy ratings was very similar. Overall, the haemostatic efficacy per day of bleeding event was assessed as excellent for 480/606 (79.1%) days, good for 104/606 (17.2%) and moderate for 21/606 (3.5%).

Children <12years:

In paediatric study CSLCT-BIO-08-52 haemostatic efficacy assessment by the investigator in 80 events in 12 subjects was excellent in 45.0% and good in 55.0%.

Major bleeding events: For 26 major bleeds the distribution of investigator efficacy ratings was similar to that overall.
Overall, the subjects assessed haemostatic efficacy per day of bleeding event as excellent for 60/76 bleeding days (78.9%) and as good for the remaining 16 bleeding days (21.1%).

Uncertainty in the knowledge about the beneficial effects
The children on routine prophylaxis experienced many more bleeds (median 23.5) during the 12 month period than the adults (median 1.0) on routine prophylaxis. Similarly, the investigator rated haemostatic efficacy as excellent in the treatment of bleeding events during the on-demand treatment periods less frequently in the paediatric <12 years of age (45%) than in the adult patients (92.1%) although the subjects' assessment per day of bleeding event was similar.
Factors which may explain the lower efficacy observed in the paediatric subjects 12 years old have not been fully explored. Ongoing post authorisation studies agreed with the MAA may provide more information.

No subjects aged from 12 to 18 years have been treated with a routine prophylaxis regimen, however pharmacokinetics in adolescents is similar to that of the adult population.

Risks

Unfavourable effects
Across the clinical studies in VWD, the percentage of subjects who experienced any treatment-emergent adverse event (TEAE) ranged from approximately 68% to 96%, however, the percentage of subjects who experienced a possibly related TEAE ranged from approximately 9% to 17%.

Overall the adverse events reported in the clinical studies were mild and none led to discontinuation.

There has been one report of development of a low responding inhibiting antibody to VWF which occurred in a paediatric subject with Type 3 VWD after 4 years on long term prophylaxis. Otherwise there have been no reports of inhibitor development either in the clinical studies or post-marketing.
Post-marketing, including previous generations of this human coagulation FVIII/VWF complex, there have been 12 reports of hypersensitivity and 1 report of anaphylactic reaction.

Incorrect dosing due to product labelling in units of FVIII and VWF has occurred in 3 subjects in the PK part of paediatric study CSLCT-08-52 and the risk for dosing errors has been addressed in the RMP

Uncertainty in the knowledge about the unfavourable effects
The number of patients with VWD in the clinical trials is small with regard to detecting uncommon adverse events such as the occurrence of inhibitor to VWD. Additional information is expected from post marketing surveillance in the PSURs.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

A VWF concentrate is currently the only effective treatment to improve haemostasis in subjects with a severe VWD phenotype.

The reduction in the number of bleeding events in a period of 12 months seen in the adult population, is clearly of value in terms of reduced morbidity and risk of life threatening mucosal bleeds, especially gastrointestinal bleeds and also joint bleeds. Subjects with Type 3 VWD also have very low circulating levels of FVIII as VWF is a carrier for FVIII in plasma and are thus prone to joint bleeds similar to patients with haemophilia A.

The aim of prophylaxis is to reduce the frequency of spontaneous and traumatic bleeds as far as possible. Current data on the 4 paediatric patients under 12 years of age who received routine prophylaxis, are limited by the small number and heterogeneity of patients, thus the magnitude of the efficacy in reducing the number and severity of bleeds experienced by these subjects while on prophylaxis, is difficult to be unequivocally demonstrated.

Concerning the on-demand treatment of bleeding events in the 12 paediatric patients <12 years of age in arm 2 of study CSLCT-BIO-08-52, haemostatic efficacy is clinically acceptable and it is of importance that in cases of haemostatic efficacy rated as excellent in 9 of 13 major mucosal bleeds which are known to be difficult to treat, was achieved. Overall, in children <12 years, approximately 97% of all bleeds in the prophylaxis arm were rated as minor compared to 73% in the on-demand arm

Unfavourable effects in terms of adverse events were minimal and in line with those expected with a coagulation factor concentrate however, administration of the product up to 3 times weekly can be seen as a burden to the patient.

Benefit-risk balance

Concerning routine prophylaxis in adult patients, the benefit in terms of reduction in the number of bleeding events is considered to be unequivocally established.

The unfavourable effects of treatment with the human coagulation factor VIII/VWF in terms of adverse events were few and most were not of clinical significance. Thus in these patients, the efficacy of routine prophylaxis can be considered to outweigh the mild adverse event profile and the burden of administrations up to 3 times weekly.

In paediatric patients <12 years, it remains difficult to assess the value of the prophylactic regimen used in this small number of patients. However adverse events reported were generally mild.

In general, any reduction in the number and severity of bleeds would have to be weighed in each individual against the burden of administration of the product up to 3 times weekly.

In patients of all ages efficacy in the treatment of bleeding events was adequate and outweighs the mild adverse event profile.

Discussion on the Benefit-Risk Balance

The haemostatic efficacy in the treatment of bleeding events in paediatric patients outweighs unfavourable effects and data confirm that dosing based on weight is appropriate also in paediatric patients.

Concerning routine prophylaxis in paediatric patients <12 years old, 3 of the 4 patients in whom prophylaxis was investigated were already on at least 12 months prophylaxis before entering the study and 3 of the 4 had Type 3 VWD. Furthermore, none of them stopped the prophylaxis regimen during the study. There are few reports available in the literature concerning routine prophylaxis in VWD but it is advocated by some

experts at an early age in subjects with a phenotype of severe VWD (Abshire et al. Prophylaxis in severe forms of von Willebrand's disease: results from the von Willebrand Disease Prophylaxis Network (VWD PN) *Haemophilia* 2013, Lassila et al Semin *Thromb Haemost* 2011) in order to prevent joint damage and to reduce the number of mucosal bleeds which are potentially serious. In a study with the VWF/FVIII concentrate Wilate, 11 patients < 6 years with phenotypically severe VWD experienced 68 bleeding events over a 12 month period on routine prophylaxis (Nowak-Göttl et al. *Haemophilia* 2013).

Thus it seems justified to view children with phenotypically severe VWD as a population in need of prophylaxis and not to exclude paediatric VWD patients <12 years old from an indication in routine prophylaxis. The data obtained from children <12 years on routine prophylaxis with Voncento are limited in that only 4 subjects received prophylaxis, although it is of value that 3 of these subjects were <6 years old during the study.

Conclusion

The benefit-risk balance for the modification of the indication to *"Prophylaxis and treatment of haemorrhage or surgical bleeding in patients with VWD, when desmopressin (DDAVP) treatment alone is ineffective or contraindicated."* is considered positive.

The initial MAA in Europe included the interim study report for study CSLCT-BIO-08-54 that presented the results up to the Month 12 visit. In this submission, the interim study report was replaced by the final study report which included an additional 12 months of prophylaxis treatment results, completing the entire 24-month treatment period of the study.

Furthermore, the MAH proposes to revise the paediatric information in various sections of the SmPC, following the completion of Study CSL-CT-08-52 in children ≤12 years old with VWD.

The benefit- risk balance for both the treatment of bleeding events and for routine prophylaxis in paediatric patients with VWD is also considered to be positive.

The dosage proposed in the paediatric population, in particular patients <12 years old is considered acceptable provided the proposal for SmPC posology Section 4.2 is modified as indicated in Section 4 "Recommendations" of this report.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II

Extension of indication for Voncento to include prophylactic treatment of patients with Von Willebrand Disease (VWD); in addition, the product information has been updated to provide data on the treatment of

paediatric patients with VWD. As a consequence, sections 4.1, 4.2, 4.4, 4.9, 5.1 and 5.2 of the SmPC have been updated. The package leaflet is updated accordingly.

Moreover, the MAH took the opportunity to correct the manufacturing sites addresses in Annex II and to make editorial changes to the product information.

The requested group of variations proposed amendments to the Summary of Product Characteristics, Labelling, Package Leaflet and Annex II.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0123/2014 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication for Voncento to include prophylactic treatment of patients with Von Willebrand Disease (VWD); in addition, the product information has been updated to provide data on the treatment of paediatric patients with VWD. As a consequence, sections 4.1, 4.2, 4.4, 4.9, 5.1 and 5.2 of the SmPC have been updated. The package leaflet is updated accordingly.

Moreover, the MAH took the opportunity to correct the manufacturing sites addresses in Annex II and to make editorial changes to the product information.

Summary

Please refer to the Scientific Discussion Voncento-H-C-2473-II-08G

6. Attachments

1. SmPC, Labelling, Package Leaflet and Annex IV (changes highlighted) as adopted by the CHMP on 25 June 2015.
2. PRAC Rapporteur´s Assessment Report on RMP circulated 18 November 2014
3. Rapporteurs initial Assessment Report circulated 19 November 2014
4. (Co)-Rapporteurs initial Assessment Report circulated 19 November 2014
5. PRAC Rapporteur´s Assessment Report as endorsed by PRAC 4 December 2014
6. CHMP Request for supplementary information as agreed by the CHMP on 18 December 2014
7. Joint Rapporteur/Co-Rapporteur Assessment Report on the responses provided by the applicant, dated 23 April 2015
8. PRAC Rapporteur´s Assessment Report as endorsed by PRAC 7 May 2015

9. Joint Rapporteur/Co-Rapporteur updated Assessment Report provided on 17 May 2015

10. 2nd CHMP Request for supplementary information as agreed by the CHMP on 21 May 2015

11. (Co)-Rapporteurs revised Assessment Report dated 12 June 2015