EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 June 2013
EMA/404213/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Voncento

HUMAN COAGULATION FACTOR VIII / VON WILLEBRAND FACTOR

Procedure No. EMEA/H/C/002493/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AHF (HP)	Anti-Haemophilic Factor (High Purity)
DDAVP	1-deamino-8-D-arginine vasopressin/desmopressin acetate
ECG	Electrocardiogram
ERA	Environmental Risk Assessment
FVIII	Human Coagulation Factor VIII
GLP	Good Laboratory Practice
Ig	Immunoglobulin
ITI	Immune Tolerance Induction
ITT	Immune Tolerance Therapy
IA	Intra-arterial
IV	Intravenous
NOAEL	No observable adverse effects level
NSB	Non-surgical bleed
P80	Polysorbate 80
PP	Per protocol
PV	Para-venous
s.e.	Standard Error
TNBP	Tri-n-butyl Phosphate
VWF	Von Willebrand factor
VWD	Von Willebrand disease

1. Background information on the procedure

1.1. Submission of the dossier

The applicant CSL Behring GmbH submitted on 23 November 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Voncento, through the centralised procedure under Article 28 of Regulation (EC) No 1901/2006. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 16 December 2010.

The applicant applied for the following indications. The wording included the indication for the strength 250 IU/600 IU and the same wording applied to 500/1200 IU and 1000 /2400 IU strengths, respectively:

Von Willebrand disease (VWD):

Prevention and treatment of haemorrhage or surgical bleeding in patients with VWD, when desmopressin (DDAVP) treatment alone is ineffective or contraindicated. Voncento 250 IU/600 IU is indicated in adults and in adolescents from 12-18 years.

Haemophilia A (congenital FVIII deficiency):

Prophylaxis and treatment of bleeding in patients with haemophilia A. Voncento 250 IU/600 IU is indicated in adults and adolescents from 12-18 years.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that human coagulation factor VIII /von Willebrand factor were considered to be known active substances.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on the applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/107/2011 on the agreement of a paediatric investigation plan (PIP).

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

The PDCO issued an opinion on compliance for the PIP P/107/2011.

Information relating to orphan market exclusivity

Similarity

The application did not contain a critical report pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, addressing the possible similarity with authorised orphan medicinal products.

Licensing status

This product is registered in Australia, New Zealand and individual countries within Asia, Central America and South America.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Pieter de Graeff Co-Rapporteur: Ian Hudson

- The application was received by the EMA on 23 November 2011.
- The procedure started on 21 December 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 9 March 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 9 March 2012.
- During the meeting on 19 April 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 19 April 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 10 October 2012.
- The final integrated GCP inspection report of the inspection carried out at one investigator site in Russia and in one investigator site in Bulgaria, between 25 and 29 June 2012 and 09 and 13 July 2012, respectively was issued on 8 October 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 27 November 2012.
- During the CHMP meeting on 13 December 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 24 April 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of outstanding issues to all CHMP members on 13 May 2013.
- During a meeting of a Blood Products Working Party on 14 May 2013, experts were convened to address questions raised by the CHMP.
- During the meeting on 30 May 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Voncento.
- A revised opinion was adopted by CHMP on 11 June 2013 by written procedure in order to adopt amendments to the CHMP assessment report.

2. Scientific discussion

2.1. Introduction

Voncento (previously Biostate) contains human plasma derived Factor VIII (FVIII) and von Willebrand factor (VWF) as active substances. VWF and FVIII are two distinct glycoproteins that circulate in plasma in the form of a non-covalently bound complex. Both factors are essential for normal haemostasis in humans. Deficiencies in FVIII or VWF lead to two distinct hereditary coagulation disorders: haemophilia A and von Willebrand disease (VWD).

Voncento belongs to the pharmacological class of hemostatic agents. The product is administered by intravenous infusion to raise FVIII and VWF levels in patients with corresponding deficiencies.

Von Willebrand Disease

Clinically, VWD is a heterogeneous group of disease variants, each characterized by distinct quantitative or qualitative abnormalities in VWF, resulting in defective or deficient function. Patients with VWD are classified into Types 1, 2, and 3. Type 1 is the most commonly documented form of VWD, accounting for 70-80% of cases, Type 2 accounts for approximately 20% of all diagnosed cases, and Type 3 the rarest form, accounts for 1-3% of cases. The main VWD classifications and subtypes can be described as follows:

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.

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 characterized 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.

In general, 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 hemostasis during bleeds or surgery. Fibrinolytic inhibitors such as tranexamic acid are frequently also used during bleeds and surgery.

Hemophilia A

Patients with hemophilia A have a hereditary deficiency of blood clotting FVIII, caused by mutations in the gene for FVIII. Inheritance of the defective gene on the X chromosome leads to hemophilia A in males and to carrier status in females.

Hemophilia A is classified as severe, moderate, or mild depending on the plasma concentration of FVIII. Severe hemophilia A is defined as having plasma FVIII:C level of < 1%, and moderate as having plasma FVIII:C level of > 1% to 5%. Depending on the severity of the disease haemophilia A can lead to a tendency to excessive haemorrhage.

Replacement therapies for FVIII deficiency consist of either plasma-derived or recombinant FVIII concentrates. So far, the main advantage of recombinant products is the higher viral safety. The major complication in the treatment of haemophilia A is the occurrence of inhibitors against FVIII (neutralising antibodies) in about 30% of patients, usually within the first 100 exposure days. Patients with severe haemophilia A are at a far higher risk to develop an inhibitor.

Treatment of VWD and haemophilia A should be supervised by a physician experienced in the treatment of haemostatic disorders. The decision on the use of home treatment for an individual patient should be

made by the treating physician who should ensure that appropriate training is provided and the use is reviewed at intervals.

The ratio between FVIII:C and VWF:RCo in a vial is approximately 1:2.4.

Details about the posology in the different conditions are provided in the SmPC.

2.2. Quality aspects

2.2.1. Introduction

Voncento is presented as a sterile, freeze-dried preparation of a human plasma protein fraction that contains the glycoprotein FVIII co-purified with VWF.

FVIII and VWF are two distinct plasma glycoproteins found associated as a non-covalent complex in plasma. Plasma FVIII has a molecular weight of 330 kDa consisting of a 80 kDa light chain and a 90-250 kDa heavy chain. VWF is a multimeric protein composed of covalently-linked dimeric subunits of about 500 kDa. Each dimer consists of two identical protein chains of about 255 kDa each, also covalently linked. In normal human plasma, the levels of FVIII and VWF are about 0.2 µg/mL and 10 µg/mL, respectively, or 1 IU/mL for each of the components. This results in a molar FVIII/VWF ratio of about 1:50 (0.7 nM/35 nM) based on monomer units.

2.2.2. Active Substance

Manufacturing Process

The Drug Substance (S400 Bulk) is defined as Human Coagulation Factor FVIII/VWF Complex, purified and stabilised with albumin. The starting material for manufacturing human FVIII/VWF complex, human plasma, complies with the Ph. Eur. monograph 0853: “Human Plasma for Fractionation” and is described in the CSL Behring Plasma Master File (EMEA/H/PMF/000001/04). The first step in the commercial manufacturing process, processing frozen plasma to cryoprecipitate is performed at CSL Behring’s manufacturing site in Bern, Switzerland. All subsequent steps are performed at CSL Biotherapies’ manufacturing facility in Broadmeadows, Australia.

The drug substance manufacturing process has sufficiently been described and a flow chart has been provided. Voncento is purified from human plasma. Briefly, to process the plasma to cryoprecipitate frozen plasma is thawed with stirring. The cryoprecipitate is isolated by centrifugation and then frozen. Frozen cryoprecipitate is thawed and a precipitation step is conducted to remove unwanted proteins. The precipitate is discarded. The FVIII supernatant undergoes a second precipitation step and the precipitate is reconstituted and then treated with solvent/detergent to inactivate enveloped viruses. The solvent detergent reagents are removed by passing the mixture through a size exclusion chromatography column. The eluate of this column is concentrated and formulated with albumin.

Process parameters and in process controls

With respect to the in process controls, the applicant had initially performed a risk assessment using own/non-standard definitions of process parameters and quality attributes. These definitions were used in further defining whether these parameters or attributes were critical or non-critical. Many obviously critical parameters were risk assessed as being non-critical. This issue was raised as a major objection. Following the request, the applicant repeated the risk assessment using ICH definitions for Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs), supplemented with own definitions to further divide non-critical quality attributes and process parameters in Key (KQAs and KPPs, affecting process performance or consistency) or Other/General (GQAs, OPPs) variables. Criticality of the quality attributes was assessed by judging whether the attribute affected safety, quality or efficacy (CQA). To evaluate

criticality of process parameters (PPs), it was determined whether the parameter affected product safety (CPP) or the product's quality attributes.This approach is acceptable. On request some adjustments were made to the criticality assessment of bioburden throughout the manufacturing process. The actions taken if limits (alert limits/action limits for critical and non-critical quality attributes; and for critical and non-critical PPs) are exceeded have been described.

Manufacturing process validation

The manufacturing process of cryoprecipitate was validated retrospectively for 30 consecutive manufacturing batches. Acceptance criteria were met. Also all acceptance criteria for the validation of the processing of manufacturing scale cryoprecipitate to Drug Substance were met. The provided data show that the process is able to produce a consistent product which meets its specifications. The equipment used to thaw the intermediates cryoprecipitate and Factor VIII precipitate has been qualified and validated. Further evaluation of the validation batches was performed to assess product impurities and contaminants (fibrinogen, fibronectin, FII), physicochemical properties (VWF multimeric analysis, FVIII immunoblotting, size exclusion HPLC and SDS page) and yield.

Manufacturing process development

Non-clinical and clinical studies performed for registration in Europe started in 2009. The main changes in the manufacturing process introduced since 2009 give no reason for concern and are covered by the validation studies. An important change introduced since 2009 concerns the addition of strengths 500 and 1000 IU FVIII/vial (100 IU/mL), by doubling the FVIII and VWF concentration without changes to excipient levels.

Voncento is manufactured from USA plasma, processed to cryoprecipitate at CSL Behring's Bern facility (product used in the pivotal clinical studies). Human Coagulation FVIII/VWF product supplied to Australia and New Zealand (and other countries within Asia) is manufactured from country specific plasma, processed to cryoprecipitate at CSL Behring's Broadmeadows facility (product used in supportive clinical trial). A combined quality-clinical major objection was raised as product characteristics (i.e. ratio VWF:RCo: FVIII, specific activity of VWF:RCo and VWF multimer distribution) changed during product development. It was unclear whether the commercial product is comparable to the product used in clinical trials. In response the applicant provided further data related to the introduction of two filtration steps to enhance the prion reduction capacity in 2007 and a comparison of the different source of cryoprecipitate. Based on the provided information, the product before and after implementation of the prion filtration step is considered comparable. The comparison of the different cryoprecipitate sources shows a difference in VWF:FVIII ratio that is maintained throughout the manufacturing process.

The difference is explained by differences in the cryoprecipitation process. From a quality point of view the drug products manufactured from Bern cryoprecipitate and Broadmeadows cryoprecipitate are therefore not fully comparable. However, this difference is not expected to influence clinical efficacy or safety. It is noted that the commercial product will only be manufactured from Bern cryoprecipitate.

Impurities

The presence of a number of protein impurities (fibrinogen, fibronectin, FII, immunoglobulins, anti-A and anti-B haemagglutinins) and non-protein impurities (process impurities) was studied at Drug Substance or Drug Product level and is sufficiently controlled. Specifications are set for fibrinogen content (Drug Substance), anti-A and anti-B haem-agglutinins, process impurities (all Drug Product). Potential contamination during processing is controlled by bio-burden measurements during the production process and virus validation studies.

Control of Drug Substance

An overview of the Drug Substance specifications has been provided. The specifications for the Drug Substance have been derived from the requirements set out in ICH Topic Q6B. This is acceptable. Batch analysis data and an adequate overview of the analytical methods used for testing the Drug Substance are provided.

Container Closure System

The container closure system for the active substance has been sufficiently described. Sterilised (gamma radiation) storage bags are used as primary packaging for the Drug Substance. Compatibility with the Drug Substance is demonstrated by stability studies and further supported by studies which were conducted to measure extractables and leachables following storage of the Drug Substance. The provided information did not give reason for concern.

Stability

Storage of the Drug Substance for the proposed shelf life and storage conditions (52 weeks at -70°C protected from light) has been appropriately validated. Stability of the cryoprecipitate under stress conditions (e.g. higher temperatures, exposure to light) has not been addressed. Upon request, this was justified by the review actions (safety, quality, identity, potency) that are taken if cryoprecipitate storage temperature conditions are breached.

2.2.3. Finished Medicinal Product

Manufacturing Process

The drug product manufacturing process consists of dilution of Drug Substance with a formulation buffer containing constituents already present in the Drug Substance, sterile filtration, filling into vials, freeze drying and heat treatment for viral inactivation. The drug product manufacturing process is in general deemed sufficiently described and validated; on request, several issues were resolved, e.g. the critical parameters/steps of the freeze drying were better laid down in the dossier. The applicant will apply the bioburden limit of 10 cfu/100 mL before sterile filtration instead of the proposed 1 cfu/mL. However, given the relatively small Drug Product batch size, a sample size of 10 mL will be used. This can be accepted. It is recommended that the applicant appropriately validates the testing method prior to implementation.

Process validation

The validation data include a number of specific studies, and the manufacture of 3 or 4 validation batches of each presentation. The validation covers the complete manufacturing process (Drug Substance and Drug Product) and shows that the process is able to produce a consistent product which meets its specifications. On request, compliance with validation requirements described in Ph. Eur. <2298> (vWF) was demonstrated. The specific validation studies gave no reason for concern.

An overview and discussion was provided of the changes made to the manufacturing process during development. This information showed that the commercial product is comparable to the product used in the pivotal clinical trials CSLCT-BIO-07-47 and CSLCT-BIO-08-54.

Control of excipients

The excipients present in the drug product are specified as Ph. Eur. and tested in accordance with the methods and requirements of the relevant Ph. Eur. monographs.

Human albumin 25% w/v is added in the drug substance manufacturing process to stabilise the drug substance. This excipient is itself a finished product, manufactured at CSL Behring in Bern, Switzerland and complying with the Ph. Eur. monograph for “Human albumin solution”. Human Albumin 25% (Alburex 25 is the brand name) is currently registered in Switzerland and within the MRP in Denmark and Italy. It

is manufactured from the same starting material as Human Coagulation FVIII/VWF Complex, covered by the CSL Behring Plasma Master File (EMEA/H/PMF/000001/04).

Human Albumin 25% is within its shelf life when used in the manufacture of Voncento. The applicant has sufficiently justified that synchronisation of the shelf life of albumin and Voncento is technically not feasible.

Control of Drug Product

An overview of the Drug Product specification and analytical test methods has been provided. A global justification for the choice of tests has been provided, and specification limits have been sufficiently justified with data: an overview of historical data and complete data for batches used in clinical studies. Some limits were tightened upon request. The applicant has provided sufficient justification that the product complies with the potency requirements of the Ph. Eur. monograph of FVIII <0275> only (FVIII estimated potency 80-120% of stated potency; VWF estimated potency 60-140% of stated potency). The request to adjust the 60-140% potency requirement for vWF potency to 80-120% in order to comply with the Ph. Eur. monograph of vWF was therefore not maintained. Upon request, the applicant re-assessed the lower release limits for vWF and concluded that the limits should be maintained. Based on the provided information it could not be determined whether this proposal is valid. However, stability data show only limited decrease of VWF:RCo potency over time suggesting that the current release limit may sufficiently ensure that batches will meet the Ph. Eur. potency requirement during the entire shelf life. Also, it is noted that the company has previously agreed to monitoring the stability batches for VWF: RCo results that fall between the 60-80% lower limit and reviewing the lower limit for VWF when sufficient batches and data points are available. It was therefore considered not necessary to request additional information.

A number of method descriptions were initially deemed too concise and upon request the Applicant submitted improved descriptions. In addition, additional validation data (especially addressing robustness) were submitted. In general, the description and validation of the analytical methods is deemed sufficient, however, a number of minor Outstanding Issues remained. These issues were appropriately addressed by the applicant. It is recommended to the applicant to implement and validate the Atomic Absorption Spectrometry method to determine sodium levels in Voncento. In addition, it is recommended that CSL Broadmeadows and Marburg participate in formal inter-laboratory proficiency studies for standardisation of FVIII potency assay.

The requested information on the International reference standards used was provided and deemed satisfactory. The protocols (including acceptance criteria) used to calibrate in-house standards have been submitted and laid down in the dossier.

Container Closure System

The drug product is supplied in a 24 mL capacity glass vial (Type I, Ph. Eur. 3.2.1) closed with a latex-free butyl rubber stopper (Type I, Ph. Eur. 3.2.9) and sealed with an aluminium seal incorporating a red plastic flip-top cap. The container closure system is sufficiently described and deemed acceptable. The product is packaged with a vial of sterile WFI and an administration kit containing a reconstitution device ('Mix2Vial').

Stability

Based on the results of the stability studies, the proposed shelf life (24 months (104 weeks) stored at or below 25°C ± 2°C, protected from light) is approvable for the Drug Product.

The applicant was requested to further substantiate this proposal with data from additional physico-chemical analysis. In response, extensive potency data and associated statistical analysis were provided. In addition, SEC-HPLC and vWF multimer analysis was performed on batches after storage of >

2 years at 2-8°C or 25°C. No differences were observed between the storage conditions. Although the ability of these assays to identify any differences may be limited, currently there are no other analytical methods available to obtain further information on stability of the product. As potency data have historically been considered acceptable as main stability indicating parameter, and some supportive SEC-HPLC and multimer data are available, the proposed shelf life can be accepted. With respect to in-use stability, a satisfactory stability study was submitted to support the proposed in-use stability period (8h).

Adventitious safety evaluation

Overall, the applicant has sufficiently evaluated the adventitious agents' safety. The solvent detergent mixing validation did not include the mixing of the detergent. Upon request, it was clarified that homogeneity of the SD solution prior to the start of the incubation cycle was validated. Measures taken to reduce the risk of virus contamination of Voncento include donor selection criteria, testing of donations and plasma pools, and two dedicated virus reduction steps in the manufacturing process (SD treatment and Dry Heat treatment of the freeze-dried product). Adequate virus validation studies have been performed to evaluate selected manufacturing steps for their capacity to remove or inactivate various viruses. Measures taken to reduce the risk of prion contamination include donor selection criteria, and two filtration steps in the manufacturing process. Investigational studies showed acceptable mean prion reduction factors over the manufacturing process of 4.0 log10 and 4.9 log10. Acceptable virus and prion safety of the excipient albumin has also been demonstrated.

With respect to virus safety, the applicant concluded that the measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV and for the non-enveloped virus HAV; the measures taken may be of limited value for the non-enveloped virus B19V. This conclusion can be endorsed.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

In general, the product Voncento is of acceptable quality. Its manufacture and control comply with current requirements and guidance. The information provided in the application demonstrates consistent batch-to-batch production of Voncento achieving a well-defined quality for the drug substance and the drug product. The quality of the drug substance and drug product is controlled by adequate test methods and specifications. Safety with regard to transmissible agents, such as human TSE and enveloped and non-enveloped viruses has been demonstrated in compliance with the relevant CHMP guidelines.

All outstanding Quality issues have been solved with a number of recommendations. The quality related issues in the SmPC have been solved.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

From a quality perspective the application for Voncento is approvable. A number of recommendations are noted. The Quality related sections of the SmPC are acceptable.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

It is recommended that:

1. The applicant monitors the stability batches for VWF:RCo results that fall between the 60-80% lower limit and reviews the lower limit for VWF when sufficient batches and data points are available.
2. The applicant appropriately validates the methodology for bioburden testing before sterile

filtration prior to implementation.

3. Both CSL Broadmeadows and Marburg will participate in formal interlaboratory proficiency studies for standardisation of FVIII potency assay.
4. The applicant fully validates and implements the Atomic Absorption Spectrometry method to determine sodium levels in Voncento and supplies the European authorities with the validation report.

2.3. Non-clinical aspects

2.3.1. Introduction

Conventional non-clinical testing has not been undertaken during development of Human Coagulation Factor VIII/VWF Complex. Studies in safety pharmacology, local tolerance and single dose toxicity have been submitted. The pharmacological studies were performed in anaesthetised, spontaneously respiring, male Beagle dogs.

GLP aspects

Safety pharmacology (study no. ZNA32393.001), local tolerance (study no. C67987) and single dose toxicity (study no. C67976) studies were Good Laboratory Practice (GLP) compliant.

2.3.2. Pharmacology

Primary pharmacodynamic studies

No primary pharmacodynamic studies have been submitted (see discussion on non-clinical aspects).

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies have been submitted (see discussion on non-clinical aspects).

Safety pharmacology programme

In-vivo safety pharmacology studies

The Applicant has submitted an IV safety pharmacology assessment of Voncento on haemodynamic and electrophysiological, cardiovascular (e.g. blood pressure, heart rate, left ventricular pressure, ECG) as well as respiratory (e.g. respiratory rate, tidal/minute volume, oxygen saturation rate) parameters in anaesthetised, spontaneously respiring, male Beagle dogs (study no. ZNA32393, GLP). There were 2 treatment groups, each consisting of 4 dogs. Animals received 0.51, 2.06, 5.14 and 12.9 ml/kg vehicle (0.9% saline) or 50, 200, 500 and 1250 IU/kg Voncento as 4 intravenous infusions (total cumulative dose of 2000 IU/kg IV). Each dose was administered over 30 min, using an infusion pump, and the dose volume for each treatment was 0.51, 2.06, 5.14 and 12.9 ml/kg, respectively. The dose levels for this study were selected based on the therapeutic dose of 50 IU/kg, the highest recommended clinical human dose of 200 IU/kg, as well as 2 supra-therapeutic doses of 500 and 1250 IU/kg. The total cumulative dose of 2000 IU/kg IV was designed to allow for a 10-fold clinical safety margin.

The administration of 50, 200, 500 and 1250 IU/kg Voncento did not markedly affect haemodynamic and electrophysiological, cardiovascular or respiratory parameters. The no observable adverse effects level (NOAEL) was considered to be a cumulative dose of 2000 IU/kg Voncento.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were submitted (see discussion on non-clinical aspects).

2.3.3. Pharmacokinetics

No pharmacokinetic studies have been submitted (see discussion on non-clinical aspects).

2.3.4. Toxicology

Table 1 Overview of toxicology studies.

Study ID	Species/ Number/ Sex/ Group	Route/ Dose (mg/kg)/(IU/kg)	GLP Compliance	Note worthy findings
C67976	Wistar Rat 5M & 5F per group	IV: Single dose 0, 50, 200, 500 and 2000	GLP	None, all animals tolerated doses up to 2000 IU/kg of Human Coagulation Factor VIII/VWF Complex
C67987	New Zealand White Rabbit 1M & 2F per group	IV, IA, PV: Single dose IV: 1 ml/rabbit IA: 1 ml/rabbit PV: 0.5 ml/rabbit	GLP	Human Coagulation Factor VIII/VWF Complex was well-tolerated following intravenous, intra-arterial and para-venous injections.
DRP029	New Zealand White Rabbit 5M & 5F per group	IV: days 1-4 & days 15-18 1 IU/rabbit	Non-GLP	None. No antigenic differences were observed between the factor VIII proteins in Human Coagulation Factor VIII/VWF Complex and AHF (High Purity)
PSR 02/10	Wistar Rat 14M & 15F	IV bolus 50, 200, 500, 2000	Non-GLP	Suitable activity levels at the highest dose of 2000 IU/kg body weight

IV: intravenous, IA: intra-arterial, PV: para-venous.

Single dose toxicity

- Study No. C67976: Single Dose Intravenous (Bolus) Toxicity Study in the Wistar Rat (GLP)

The objective of the study was to assess acute toxicity following a single IV dose of Voncento injection into the tail vein to Wistar rats of both sexes at dose levels of 50, 200, 500 and 2000 IU FVIII per kg body weight. A control group was treated similarly with 0.9% saline. Each group consisted of 5 animals of each sex, including an additional 6 per sex (2 per sex for the control group) for plasma level determination/toxicokinetic evaluations. Animals were examined for clinical signs of toxicity, food consumption and change in body weight.

Analysis of hematology parameters six days following the treatment showed signs of a mild anaemia in males treated with 200, 500 or 2000 IU/kg, such as reduced numbers of erythrocytes and an increase in the numbers of early reticulocytes. Nonetheless, a clear dose-dependency was lacking. Also in females treated with the test item, slightly reduced erythrocyte numbers were noted, but a statistical significant effect was only seen in the group treated with 200 IU/kg. These effects might be related to the presence of a high protein load due to high concentrations of the test item. As no clinical signs of toxicity were noted during and after the treatment and all animals were in a good condition at the end of the 6-day

observation period, the small changes in haematology parameters were not considered of adverse nature.

In males treated with 2000 IU/kg, the plasma concentration of potassium was slightly increased. As the treatment with the test item was generally well tolerated by these animals, this minor change is not considered adverse. No test item-related changes in urinary parameters were evident at the end of the observation period.

Slightly increased spleen weights were noted in both sexes at all dose levels at the end of the observation period. However, the changes were only small, mostly without achieving statistical significance. As there was also no microscopic correlate for this finding it is considered not of adverse nature.

Finally, there was no histological evidence of toxic effects in a variety of organs and tissues in animals treated once with the test item at 500 or 2000 IU/kg. At the injection site, no signs of local toxic effects of the test item were observed.

In conclusion, based on the results of this study, no local or systemic adverse effects of Voncento were evident during a 6-day observation period after single intravenous injection of 50, 200, 500 or 2000 IU/kg into the tail vein of Wistar rats of both sexes.

Repeat dose toxicity

No repeat dose toxicity studies have been submitted (see discussion on non-clinical aspects).

Genotoxicity

No studies on the genotoxic potential of Human Coagulation Factor VIII/VWF Complex have been submitted (see discussion on non-clinical aspects).

Carcinogenicity

No carcinogenicity studies have been submitted (see discussion on non-clinical aspects).

Reproduction Toxicity

No reproduction toxicity studies have been submitted (see discussion on non-clinical aspects).

Toxicokinetic data

- Single dose pharmacokinetic study of Voncento after intravenous administration to rats (Study no.: PSR 02/10)

A toxicokinetic study in rats applying dosages between 50 and 2000 IU/kg was submitted.
Pharmacokinetic analysis of Voncento after intravenous administration of doses between 500 and 2000 IU/kg demonstrated an increase in the plasma levels of coagulation factor VIII activity. At the highest dose of 2000 IU/kg body weight suitable activity levels were found, hence adequate exposure to Voncento could be demonstrated.

Local Tolerance

- Local tolerance study in rabbits 4 days after intravenous, peri-venous and intra-arterial injection (Study no. C67987, GLP)

Local reaction after unintentional administration of Voncento through the peri-venous (PV) or intra-arterial (IA) route of administration was assessed in the New Zealand White rabbit and compared to

the intended intravenous route of administration, with the drug product intended to be marketed. A total of 9 rabbits were included in the study, 3 animals per route of administration (1 male and 2 female).

Each rabbit was administered with either 0.5 ml Voncento (49 IU/animal, 16-24 IU/kg, PV route) or with 1 ml (97 IU/animal, 32-48 IU/kg, IV and IA) injected into the right ear. The left ear served as the control as it was injected with vehicle using the same volume injected for Voncento. Clinical signs were recorded twice daily on test day 1, 2, 3 and 4. There were no signs of toxicity or ill health in any treated animal during the observation period. There were slight observations of increased erythema in all the PV treated rabbits on days 3 and 4. No changes were seen for IV or IA rabbits. Macroscopically, there were no gross lesions. In the microscopic findings noted after the three types of injection, there were no substantial differences between right ear (test item) and left ear (control item). Changes seen in macropathological and histological findings were considered related to the different routes of administration rather than to be an effect caused by Voncento.

Other toxicity studies

Immunogenicity

- Study No DRP029: Evaluation of Neoantigen Generation in Voncento using a Rabbit Immunogenicity Model (non-GLP)

A study to detect possible differences in the immunological properties (formation of new epitopes) between AHF (High Purity, HP) and Voncento was performed in rabbits according to the method published by Ronneberger (1986).

Groups of 5 adult New Zealand White rabbits (male and female) were immunised intravenously daily with 1 IU Factor VIII of either AHF (High Purity) or Voncento on days 1-4 and 15-18. Rabbits were bled via the marginal ear vein before the initial immunisation (pre-bleed) and also one week after the final immunisation. The serum was then isolated and the immunoglobulin (Ig) fraction from rabbit sera was purified by ammonium sulphate precipitation. Immunoglobulins from rabbits immunised with AHF (High Purity) and Voncento was analysed by double immunodiffusion (Ouchterlony) and enzyme-linked immunosorbent assay (ELISA) for reactivity with the respective immunogen and alternate antigen.

Double immunodiffusion: All immune Ig fractions from rabbits immunised with Voncento demonstrated reactivity with both Voncento antigen and AHF (High Purity) antigen, and vice versa. Antibody reactivity of all immune Ig with the immunogen was completely removed by preincubation with the alternate antigen.

Elisa: Reduction in reactivity of rabbit Ig to immobilised antigen was observed for all antigen-absorbed samples with the greatest reduction occurring with the highest amount of antigen used. Even at the lowest concentration of antigen significant reduction in antibody binding was observed compared to the non-absorbed positive control. In addition, identical reduction in reactivity of each Ig was seen after absorption with the immunogen and with the alternate antigen.

The results of the rabbit immunogenicity model did not reveal any changes in the immunological characteristics of Voncento [as compared to AHF (HP)] suggesting that the manufacturing process did not induce the formation of new epitopes or make the product more immunogenic than AHF (HP). No antigenic differences were observed between the FVIII proteins in Voncento and AHF (HP).

Impurities

No studies on impurities have been submitted (see discussion on non-clinical aspects).

2.3.5. Ecotoxicity / environmental risk assessment

No environmental risk assessment (ERA) has been submitted (see discussion on non-clinical aspects).

2.3.6. Discussion on non-clinical aspects

No studies on the primary and secondary pharmacodynamic effects of Human Coagulation Factor VIII/ VWF Complex have been submitted. The complex is an endogenous human compound with known pharmacological action, and the lack of studies is therefore acceptable.

The newly conducted safety pharmacology, single dose toxicity and local tolerance studies were conducted in compliance with GLP. The additional toxicokinetics study was not GLP compliant. This is accepted due to the nature of the study. The neoantigen generation study was also not performed in compliance with GLP. However, the study was scientifically sound and adequate conclusions could be drawn.

No treatment-related findings were observed in the safety pharmacology study on cardiovascular and respiratory parameters in beagle dogs.
No pharmacodynamic drug interaction studies were performed. Animal data are not needed because human plasma derived factor VIII/VWF factor concentrates have a well-established physiologic effect in humans.

No non-clinical pharmacokinetic studies have been performed. These studies are not considered necessary due to the human origin of Human Coagulation Factor VIII/VWF Complex, the relatively long history of its clinical use, and the evaluation of the pharmacokinetic aspects of Human Coagulation Factor VIII/ VWF Complex in clinical trials.

Voncento was well tolerated in male and female rats up to 2000 IU/kg. Slight effects were seen in some parameters, including mild anaemia and increased reticulocytes, increased plasma potassium in males, and increased spleen weights. These effects can all be attributed to increased protein load, leading to nonspecific toxicity. No new or unexpected toxicity was observed.

Voncento contains FVIII and VWF as active ingredients which are derived from human plasma and act like endogenous constituents of plasma. Non-clinical studies with repeated dose applications (chronic toxicity and carcinogenicity) cannot be reasonably performed in conventional animal models due to the development of antibodies following the application of heterologous human proteins (see SmPC section 5.3). Moreover no studies on the genotoxic potential of Human Coagulation Factor VIII/VWF Complex can be performed as the constituents of Human Coagulation Factor VIII/VWF Complex are physiological human plasma proteins and potential genotoxicity is not expected. This is in line with ICH S6 (R1) guideline for preclinical safety evaluation of biotechnology-derived pharmaceuticals.

No studies for reproductive and developmental toxicity have been submitted. Adverse effects on fertility, postnatal development and reproduction as well as teratogenic effects are not expected in humans. Experience in the treatment of pregnant or lactating women is not available. Voncento should be administered to pregnant or lactating women only if benefit outweighs the risks (see SmPC section 4.6 and Risk Management Plan) taking into consideration that delivery confers an increased risk of haemorrhagic events in these patients.

A separate toxicokinetic experiment was performed. Adequate exposure to the complex was demonstrated in rats in line with the results from the single dose toxicity study.

Local tolerance has been assessed in a dedicated local tolerance study in rabbits. The Applicant has justified the use of rabbits for this study based on their sensitivity and widespread use to assess local tolerance. Voncento is considered to be well tolerated in rabbit at clinically relevant doses.

The Applicant has used a rabbit immunogenicity model to compare the immunogenic properties of AHF (High Purity) and Voncento and identify the possible formation of new epitopes in factor VIII molecules of Voncento generated during the manufacturing process. There are no concerns that new epitopes are generated with the Voncento manufacturing process as compared to AHF (HP). Nevertheless, the issue of neoantigen formation and subsequent development of inhibitory antibodies in treated patients should be monitored carefully in the clinic (see Clinical aspects).

The process reagents tri-n-butyl phosphate (TNBP) and polysorbate 80 (P80) (utilized as the solvent/detergent mixture in the first virus inactivation step) have been widely used for viral inactivation. Based on the maximum recommended dose of 200 IU/kg/day of Human Coagulation Factor VIII/VWF Complex a patient may receive up to 100 µg P80/kg/day for the 100 IU/ml strengths and 200 µg P80/kg/day for the 50 IU/ml strengths. The maximum level of P80 from Human Coagulation Factor VIII/VWF Complex is 0.4% of the dose that caused a transient drop in the blood pressure in cats, rabbits and monkeys (Moore J, 1984). Thus, total anticipated exposure to P80 from Human Coagulation Factor VIII/VWF Complex are well below the minimum dose that caused toxicity in animals. Based on the maximum recommended dose of Human Coagulation Factor VIII/VWF Complex a patient may receive up to 20 µg TNBP/kg/day for the 100 IU/ml strengths and 40 µg TNBP/kg/day for the 50 IU/ml strengths. These dose levels are well below the minimum dose that caused toxicity in animal studies. The maximum level of TNBP from Human Coagulation Factor VIII/VWF Complex is 0.1% of the LD50 in mice via the IV route. Daily administration of TNBP at concentrations 10 times higher than in Human Coagulation Factor VIII/VWF Complex have been shown to cause no pathology when administered IV to rabbits for 13 weeks (Vandekar M, 1957). In conclusion, no safety issues are expected due to these excipients.

The applicant 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.

2.3.7. Conclusion on the non-clinical aspects

Voncento contains FVIII and VWF as active ingredients which are derived from human plasma and act like endogenous constituents of plasma. Preclinical studies with repeated dose applications (chronic toxicity and carcinogenicity) cannot be reasonably performed in conventional animal models due to the development of antibodies following the application of heterologous human proteins. No studies on the genotoxic potential of Human Coagulation Factor VIII/VWF Complex were performed as the constituents of Human Coagulation Factor VIII/VWF Complex are physiological human plasma proteins and potential genotoxicity is not expected.

This information is included under section 5.3 of the SmPC.

Animal reproduction studies have not been conducted with Voncento. Experience in the treatment of pregnant or lactating women is not available. Voncento should be administered to pregnant or lactating women only if clearly indicated (see SmPC section 4.6 and Risk Management Plan).

2.4. Clinical aspects

2.4.1. Introduction

The claimed indications for Voncento are for the prevention and treatment of haemorrhage or surgical bleeding in patients with VWD, when desmopressin (DDAVP) treatment alone is ineffective or contraindicated and for the prophylaxis and treatment of bleeding in patients with hemophilia A, in adults and adolescents from 12-18 years.

GCP

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

A GCP inspection of two investigator sites of study SLCT–BIO -08-54 was requested and conducted. As a result of the identified GCP inspection findings, the applicant conducted a series of activities including independent site audits (incl. patient selection, dosing, source data verification), and database audits against source documentation, for a majority of trial sites. The documentation and responses provided by the Applicant after the inspection upon request by the Rapporteurs (including the results of internal audit and re-analysis) were considered satisfactory and the CHMP concluded that the findings identified did not have a significant impact on key trial parameters such as diagnosis or efficacy and safety evaluations.

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.

2.4.2. Pharmacokinetics

The studies provided in support of PK for both indications are presented in the table 2 below.

- **Table 2: Studies providing pharmacokinetic data on human coagulation FVIII/VWF complex in subjects with hemophilia A and VWD.**

Study	phase	subject	study design	product and dose	PK assessment
BIO-07-47	II 2009-2010	haem. A N=17 PK [16 pts in PK analysis, 17 pts in PK safety]	Double-blind, randomised, cross-over (initial PK); open-label, uncontrolled (efficacy component, repeat PK)	Voncento SP FVIII 50 IU/kg Voncento RP FVIII 50 IU/kg	single dose comparative PK and repeat dose for Voncento SP
BIO-95-30	II 1998	haem. A N=16	Open-label, Multi-centre	Voncento AU FVIII 50 IU/kg	single dose
BIO-95-41	II/III 1998-1999	haem. A N=16 PK -8 pts for repeat PK	Open-label, uncontrolled, multi-centre	Voncento AU FVIII 50 IU/kg	single dose and repeat dose
BIO-08-54	II/III 2009-2011	VWD N=15 PK	Open-label multi-centre study	Voncento SP VWF 80 IU/kg	single dose and repeat dose
BIO-00-75	I 2003	VWD N=12	Single-blind, randomised, cross-over, multi-centre	Voncento AU VWF 60 IU/kg AHF-HP VWF 60 IU/kg	single dose comparative PK

- **Study BIO-07-47 (Hemophilia A) - Pharmacokinetic data**

The pivotal PK, safety, and efficacy study BIO-07-47 was conducted in Eastern Europe in 2009/2010 (see Main Studies for detailed description and efficacy results).

Subjects who had been diagnosed with hemophilia A and had FVIII levels of ≤1% in the absence of factor replacement according to their medical history were included. Subjects who were actively bleeding, or had received an infusion of any FVIII product, whole blood, plasma or desmopressin acetate in the 4 days prior to day 1, or had a known history of FVIII inhibitors were excluded from PK part.

The study included a PK component with an initial PK assessment in a double-blind, crossover design to assess the bioequivalence between Voncento reference product (RP) and Voncento study product (SP), and a repeat PK assessment about 6 months after the initial assessment (Voncento SP). Voncento reference product (RP), was the initial product, used in clinical studies until May 2003, and Voncento study product (SP) was the product with an additional filter (a filtration step to enhance prion clearance), used as the IMP since March 2009 (start of the clinical development of the IMP in Europe).

Voncento dose of 50 IU/kg was to be administered on Days 1 and 8. Repeat PK assessment included 15 subjects who had initial PK assessment and consisted of a single dose of 50 IU/kg Voncento SP on Day 180.

Blood samples for the PK assessment for comparison of Voncento RP and Voncento SP were taken on Days 1 and 8, at pre-infusion and at 0.5, 2, 4, 8, 12, 24, 28, and 48 h after the end of the infusion of Voncento. FVIII plasma concentrations were determined by a central laboratory.

Results

A total of 81 subjects, including 3 adolescents (as required according to the approved PIP EMEA-000312-PIP01-08), were enrolled into the study; 17 adult subjects participated in the PK component (16 were evaluable for the initial PK assessment and 15 for the repeat PK assessment). All subjects of the PK population were male Caucasians and mean age was 36.5 years with a range of 18 to 57 years.

A comparison of FVIII pharmacokinetic parameters following the initial administration of Voncento SP in 16 subjects with severe hemophilia A is shown in table 3.

Table 3: Summary of PK parameters –Part 1(study CSLCT-BIO-07-47)

PK parameter	Biostate SP N=16	Biostate RP N=16
Incremental recovery [kg/mL]		
Mean (SD)	0.021 (0.006)	0.023 (0.005)
Median (range)	0.021 (0.011 - 0.032)	0.023 (0.009 - 0.031)
Geometric mean	0.021	0.022
CV%	26.3	23.9
Half-life [h]		
Mean (SD)	13.40 (2.53)	13.07 (1.82)
Median (range)	13.74 (8.78 - 18.51)	13.04 (9.84 - 16.10)
Geometric mean	13.17	12.95
CV%	18.9	13.9
AUC_{0-48} [h*IU/mL]		
Mean (SD)	13.79 (3.79)	14.34 (3.63)
90% CI for the mean	[12.14, 15.45]	[12.75, 15.94]
Median (range)	13.09 (7.04 - 21.79)	13.88 (6.30 - 19.55)
Geometric mean	13.29	13.84
90% CI for the geometric mean	[11.71, 15.08]	[12.18, 15.73]
CV%	27.5	25.3
MRT [h]		
Mean (SD)	16.96 (3.68)	16.69 (2.55)
Median (range)	16.62 (11.29 - 26.31)	16.54 (12.24 - 20.33)
Geometric mean	16.61	16.50
CV%	21.7	15.3
C_{max} [IU/mL]		
Mean (SD)	1.07 (0.28)	1.13 (0.27)
90% CI for the mean	[0.94, 1.19]	[1.01, 1.25]
Median (range)	1.07 (0.57 - 1.57)	1.14 (0.43 - 1.55)
Geometric mean	1.03	1.09
90% CI for the geometric mean	[0.91, 1.17]	[0.95, 1.25]
CV%	26.4	23.9
t_{max} [h]		
Mean (SD)	0.81 (0.94)	0.50 (0.01)
Median (range)	0.50 (0.42 - 4.03)	0.50 (0.48 - 0.50)
Geometric mean	0.61	0.50
CV%	116.7	1.4
C_{min} [IU/mL]		
Mean (SD)	0.060 (0.028)	0.061 (0.024)
Median (range)	0.062 (0.021 - 0.111)	0.061 (0.020 - 0.102)
Geometric mean	0.053	0.055
CV%	46.7	40.1
Total clearance [mL/(h*kg)]		
Mean (SD)	3.92 (1.22)	3.78 (1.33)
Median (range)	3.82 (2.30 - 7.11)	3.60 (2.56 - 7.94)
Geometric mean	3.76	3.61
CV%	31.2	35.3
V_{ss} [mL/kg]		
Mean (SD)	65.33 (20.65)	62.57 (23.12)
Median (range)	61.16 (35.07 - 113.06)	54.86 (43.28 - 127.07)
Geometric mean	62.49	59.61
CV%	31.6	37.0

- **Study BIO-08-54 (Von Willebrand Disease) - Pharmacokinetic data**

Study BIO-08-54 was an open-label multi-centre study to assess the PK, efficacy, and safety of human coagulation FVIII/VWF complex in previously treated subjects with severe VWD (VWF Ristocetin Cofactor

Activity [VWF:RCo] <15% at screening or a documented history of VWF:RCo <10%) for whom 1-deamino-8-D-arginine vasopressin, desmopressin acetate (DDAVP) treatment had been ineffective, contraindicated, or not available (see Main Clinical Studies). Pharmacokinetics was studied after the first administration of Voncento 80 IU/kg in 15 subjects with VWD.

Blood samples were collected to assess the PK for VWF:RCo, Von Willebrand factor: Antigen (VWF:Ag), Von Willebrand factor: Collagen Binding capacity (VWF:CB), and factor VIII coagulant activity (FVIII:C) following an initial single dose of 80 IU/kg VWF:RCo at pre-infusion, and at 15 min, 1, 3, 6, 8, 12, 24, 30, 48 and 72 h post-infusion. The PK parameters calculated for VWF and FVIII included half-life, incremental recovery, AUC, C_{max}, t_{max}, C_{min}, Cl, V_{ss}, and MRT. In addition, the PK samples obtained from the Type 3 VWD subjects (prior to dosing, 15 min and 6 h after infusion) were used to investigate the multimer distribution of VWF.

Repeat PK assessment occurred at least 6 months after the initial assessment (after at least 2 further doses of human coagulation FVIII/VWF complex and at least 5 days after the last Voncento SP dose) and was performed in the 8 subjects with Type 3 VWD who participated in the initial PK assessment. The Voncento SP dose, blood sampling time points, and PK parameters were the same as for the initial PK assessment.

Results

Pharmacokinetic results are summarised in Table 4.

Table 4: Summary of Baseline-adjusted VWF and FVIII:C PK parameters (PK population)

	VWF:RCo				VWF:Ag				VWF:CB				FVIII:C			
parameter	N	Mean	SD	range	N	Mean	SD	range	N	Mean	SD	range	N	Mean	SD	range
Incremental recovery (kg/mL)	12	0.017	0.002	0.01-0.02	12	0.018	0.002	0.01-0.02	12	0.020	0.004	0.02-0.02	12	0.025	0.006	0.02-0.04
Half-life (h)	8	13.7	9.2	6.1-35.1	12	18.3	4.0	11.4-27.0	12	16.0	4.6	9.4-25.1	10	28.0	15.7	7.7-57.5
AUC_{0-72} (h*IU/mL)	12	17.7	9.7	12.7-22.7	12	37.8	13.3	22.6-64.7	12	24.8	8.8	14.8-41.1	11	34.0	16.2	13.2-66.8
MRT (h)	8	14.0	5.0	8.6-25.5	12	23.6	5.0	15.3-33.6	12	20.0	4.4	11.6-28.6	10	43.1	22.1	15.6-85.1
C_{max} (IU/mL)	12	1.65	0.63	0.93-3.36	12	2.29	0.59	1.52-3.66	12	1.68	0.50	1.04-2.66	12	0.96	0.25	0.57-1.32
T_{max} (h)	12	0.25[a]		0.25-1.03	12	0.25 [a]		0.25-1.00	12	0.25 [a]		0.25-1.00	12	1.00 [a]		0.25-30.00
C_{min} (IU/mL)	12	0.01	0.01	0.00-0.03	12	0.10	0.05	0.02-0.17	12	0.05	0.02	0.02-0.09	12	0.21	0.18	0.03-0.59
Total clearance (mL/(h*kg)	12	6.09	1.66	3.06-9.32	12	3.57	0.69	2.61-4.78	12	3.53	0.89	2.32-4.77	11	1.33	0.59	0.62-2.47
V_{ss} (ml/kg)	8	74.8	35.3	44.7-158.0	12	82.8	18.6	64.5-128.4	12	68.6	15.7	47.5-93.7	10	48.1	15.3	24.8-72.9

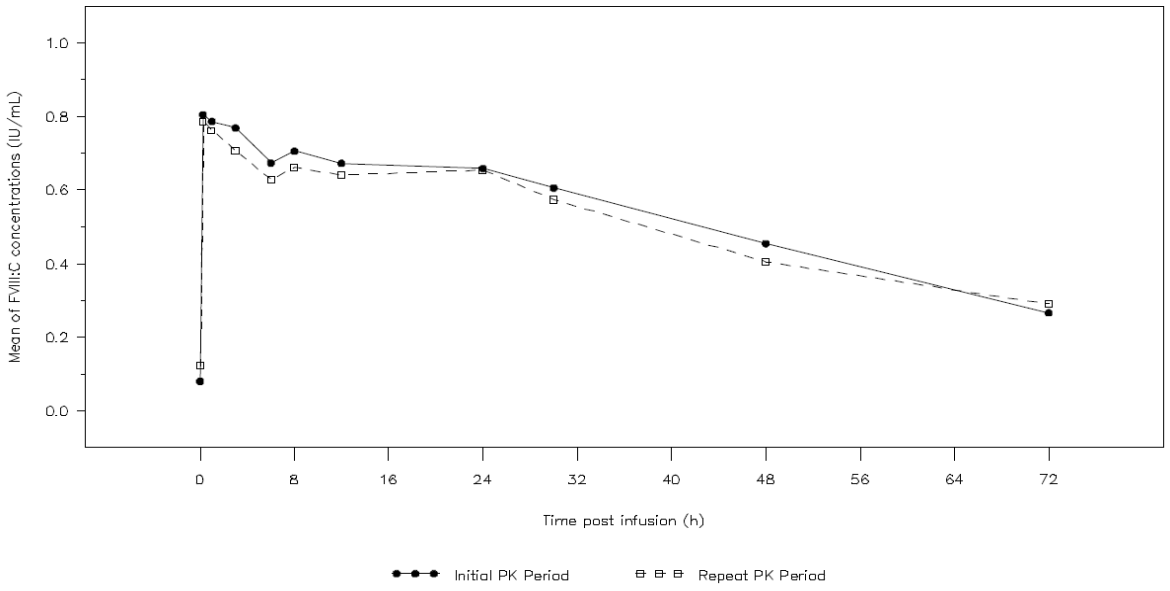
[a] median

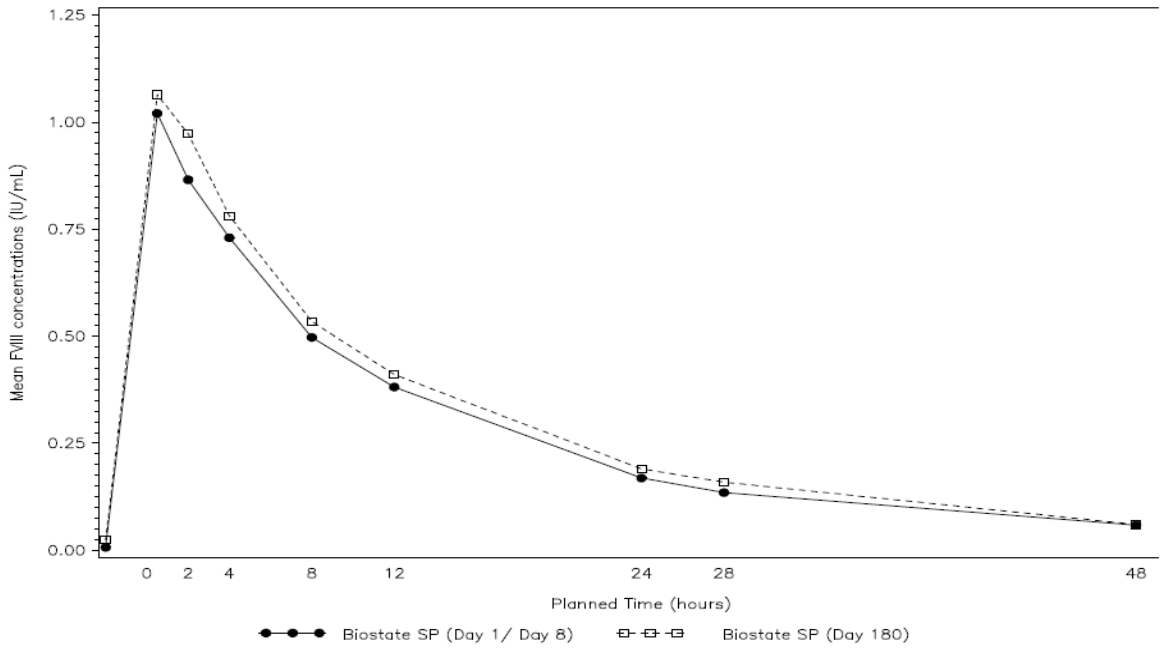
AUC = area under the curve; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; IU = International Unit; MRT = mean residence time; N = number of subjects; SD = standard deviation; t_{max} = time the maximum concentration occurs; V_{ss} = volume of distribution at steady state; 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

The relative HMW VWF of Voncento compared to normal human plasma was on average 86%. The relative expression of HMW VWF multimers in VWD patients after infusion of Voncento was approximately 10% (using a semi-quantitative multimer analysis).

- **Analysis across studies: Study BIO-08-54 (Von Willebrand Disease) and Study BIO-07-47 (Hemophilia A)**

Figure 1: Mean adjusted FVIII:C concentration (IU/mL) – initial and repeat PK in subjects with VWD type 3 study BIO-08-54 (first panel) following iv infusion with 80 IU/kg VWF:RCo (=33 IU/kg FVIII) and in hemophilia A subjects following i.v. infusion with 50 IU/kg FVIII (second panel).





Dose proportionality and time dependencies

No studies were submitted (see discussion on clinical pharmacology).

Special populations

No special populations have been studied (see discussion on clinical pharmacology).

Pharmacokinetic interaction studies

No studies were submitted (see discussion on clinical pharmacology).

Pharmacokinetics using human biomaterials

No studies were submitted (see discussion on clinical pharmacology).

2.4.3. Pharmacodynamics

No studies were submitted (see discussion on clinical pharmacology).

2.4.4. Discussion and conclusions on clinical pharmacology

Pharmacodynamic studies were not conducted for human coagulation FVIII/VWF complex since the pharmacodynamics of the FVIII/VWF complex in humans is well documented and its efficacy has been demonstrated.

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 hemostasis in humans. A deficiency or abnormality in VWF can interfere with the formation of the temporary platelet plug (primary hemostasis) and also affect the normal survival of FVIII, which ultimately can interfere with the production of fibrin and stabilization of the clot (secondary hemostasis). Individuals with VWD, therefore, have difficulty in forming blood clots and as a result, may bleed for longer periods of time than normal. Bleeding can sometimes occur spontaneously. In hemophilia A, primary hemostasis is normal, but secondary hemostasis is impaired because the primary hemostatic plug is not stabilized due to the FVIII deficiency and re-bleeding occurs.

VWF is a multimeric, adhesive, plasma glycoprotein that is synthesized in megakaryocytes and endothelial cells as a 260 kDa precursor. The precursor (ie, pro-VWF) forms intracellular dimers, which are in turn glycosylated and then further associated into multimers ranging from 500 to 20,000 kDa, before being released into the plasma as ultra-large VWF multimers.

Exogenously administered human plasma-derived VWF behaves in the same way as endogenous VWF. Administration of VWF allows correction of the haemostatic abnormalities exhibited by patients who suffer from VWF deficiency (VWD) at two levels:

- VWF re-establishes platelet adhesion to the vascular sub-endothelium at the site of vascular damage (as it binds both to the vascular sub-endothelium and to the platelet membrane), providing primary haemostasis as shown by the shortening of the bleeding time. This effect occurs immediately and is known to depend to a large extent on the level of polymerisation of the protein.
- VWF produces delayed correction of the associated FVIII deficiency. Administered intravenously, VWF binds to endogenous FVIII (which is produced normally by the patient), and by stabilising this factor, avoids its rapid degradation.

  Because of this, administration of pure VWF (VWF product with a low FVIII level) restores the FVIII:C level to normal as a secondary effect after the first infusion with a slight delay.
- Administration of a FVIII:C containing VWF preparation restores the FVIII:C level to normal immediately after the first infusion.

In hemophilia A, exogenously administered human plasma-derived FVIII behaves in the same way as endogenous FVIII. The FVIII/VWF complex consists of two molecules (FVIII and VWF) with different physiological functions. When infused into a haemophiliac patient, FVIII binds to VWF in the patient's circulation. Activated FVIII acts as a cofactor for activated factor IX accelerating the conversion of factor X to activated factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed.

High molecular weight (HMW) multimers of VWF seem to be essential for its hemostatic function. In VWD type 3 subjects after administration of Voncento SP, VWF high molecular weight multimers were present as approximately 10% of total VWF multimers, which seemed low compared to normal plasma (~25% HMW). Nevertheless, based on the observed hemostasis in study BIO-08-54, the HMW VWF multimer expression appeared to be high enough to exert an adequate clinical effect.

Repeat PK results as seen in pivotal study CSLCT-BIO-07-47 and supportive study CSLCT-BIO-95-41 were comparable. Concordance between initial and repeat PK of mean incremental recovery (0.021 and 0.022 kg/mL) and mean half-life (13.49 and 13.16 h) indicated that inhibitors had not developed with repeated exposure to human coagulation FVIII/VWF complex during the conduct of study CSLCT-BIO-07-47.

The overall PK data are considered to comply with the CHMP guidelines for both Factor VIII and VWF products. In addition PK studies demonstrated comparability between Voncento SP and Voncento RP and results were comparable to literature reports.

The PK of FVIII:C was rather different in VWD type 3 subjects compared to haemophilia A subjects. FVIII:C levels remained high longer in VWD subjects probably due to stabilisation of the endogenous produced FVIII by the added VWF complex as production of FVIII is not impaired in VWD. Such an effect on FVIII:C in VWD subjects is product specific. In VWD, usually 40-80 IU/kg of von Willebrand factor (VWF:RCo) and 20-40 IU/kg of FVIII:C are recommended to achieve haemostasis and the appropriate dose should be re-administered every 12-24 hours. At 12-24 hours FVIII:C concentrations are still at maximum levels, therefore, accumulation may occur after repeat dosing and may thus increase the risk of thromboembolic events.

When using a FVIII-containing VWF product, the treating physician should be aware that continued treatment may cause an excessive rise in FVIII:C. In patients receiving FVIII-containing VWF products, plasma levels of FVIII:C should be monitored to avoid sustained excessive FVIII:C plasma levels which may increase the risk of thrombotic events, and antithrombotic measures should be considered (see SmPC section 4.3).

A statement that especially FVIII:C levels should be closely monitored especially when high doses of Voncento (e.g. during surgery in case of Von Willebrand disease) are needed, is included in section 4.2 of the SmPC and the risk of thromboembolic complications is highlighted in section 4.4 of the SmPC.

No interactions of human von Willebrand factor and human coagulation factor VIII with other medicinal products have been reported (see SmPC section 4.5).
No pharmacokinetic data are available in patients younger than 12 years (see SmPC section 5.2).

2.5. Clinical efficacy

2.5.1. Dose response studies

See main studies.

2.5.2. Main studies

- **Study CSLCT-BIO-08-54 (von Willebrand's disease indication)**

Study CSLCT-BIO-08-54 (NCT00941616) was an open-label, multi-centre study design to assess the pharmacokinetics, efficacy and safety of human coagulation factor VIII / von willebrand factor in subjects with Von Willebrand disease.

Methods

Study Participants

Main inclusion criteria:

- Male and female subjects who were at least 12 years of age.
- 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.
- Where DDAVP treatment was ineffective, contraindicated, or not available.
- Required a VWF product for prophylactic therapy or to control a non-surgical bleed (NSB) event.

Main exclusion criteria:

For participants of the PK component:

- Were actively bleeding immediately prior to the initial PK period.
- Received DDAVP or a VWF product in the 5 days prior to their first dose of study product.
- Had Type 2B, 2N, or 2M VWD.

For all subjects:

- 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.
- Received aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) within 7 days prior to their first dose of study product.
- Known history of or were suspected to have VWF or FVIII inhibitors.
- Subjects with impaired liver function at screening, i.e. bilirubin >1.5 x upper limit of normal (ULN), and/or aspartate transaminase (AST)/alanine transaminase (ALT) >2.5 x ULN (referring to the limits of the laboratory that performed the determination).

Treatments

The study consisted of 3 periods (Figure 2):

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.

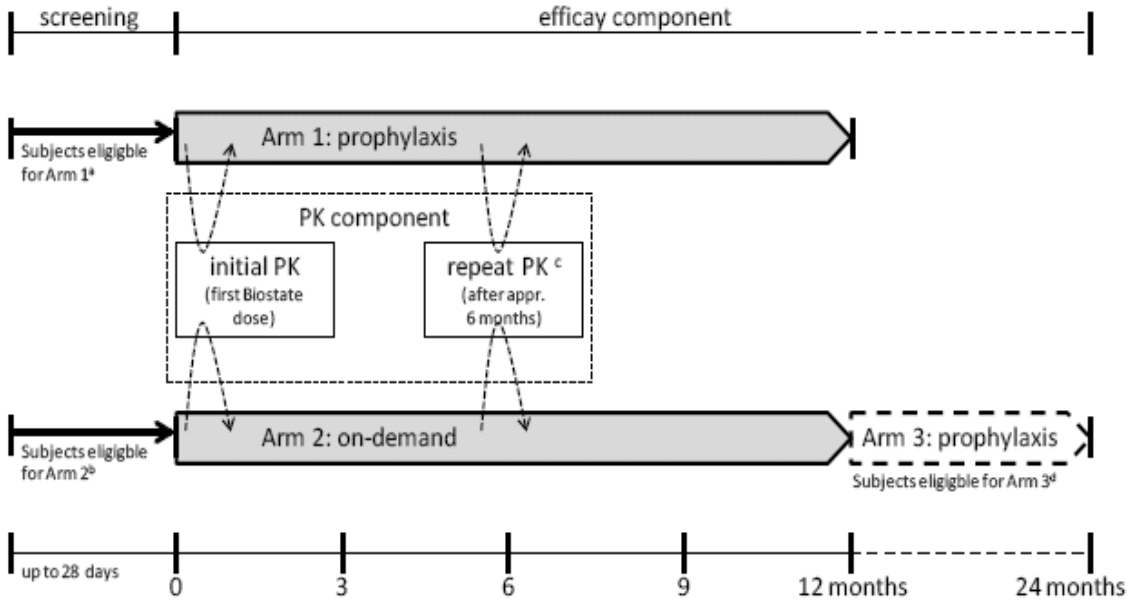
3. Efficacy component (all subjects) of up to 12 or 24 months; depending on the treatment arm subjects participated in:

Arm 1 (prophylaxis arm): Subjects were to receive Voncento as prophylaxis therapy for 12 months. 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 and received Voncento as part of a prophylaxis regimen as determined by the severity of their disease for a period of 12 months. Arm 1 subjects completed the study with a final visit at month 12.

Arm 2 (on-demand arm): Subjects were to receive Voncento as on-demand therapy for 12 months. Subjects who were not on a set prophylaxis regimen with a VWF product at the time of study entry, and who required a VWF product for the treatment of NSB events (spontaneous or trauma-induced), were enrolled into Arm 2 and commenced using Voncento as on-demand therapy for the treatment of NSB events. At the Month 12 visit, Arm 2 an assessment was made, based on the extent and location of any bleeding events, for eligibility to be switched to a set prophylaxis regimen with Voncento for an additional 12 months (Arm 3). Subjects who were not eligible to enter Arm 3 completed the study with the final visit at month 12.

Arm 3: Subjects, who completed treatment (on-demand therapy with Voncento) in Arm 2 and who at the Month 12 visit qualified to be switched to a set prophylactic regimen according to the criteria prespecified in the study protocol, entered Arm 3 and started Voncento treatment as prophylaxis therapy for an additional 12 months. The prophylaxis regimen was determined by the extent and location of NSB events during the preceding 12-month on-demand therapy period. The total treatment duration for subjects in Arm 3 was up to 24 months.

Figure 2: Study design chart



PK = pharmacokinetic(s)
[a] subjects being treated on a set prophylaxis regimen with a VWF product, or when prophylaxis treatment was justifiable in the opinion of the investigator at the time of study entry.
[b] subjects who were not on a set prophylaxis regimen with a VWF product at the time of study entry but who required a VWF product for treatment of NSB events.
[c] Type 3 VWD PK subject only
[d] Subjects who completed treatment in Arm 2 and who at the Month 12 visit qualified to be switched to a set prophylactic regimen

In the PK component of the study, subjects received 80 IU/kg VWF:RCo based on the subject's body weight.

For each subject in the efficacy component of the study, the frequency and dose of Voncento was determined by the Investigator (Table 5). The dose was based on the subject's clinical condition, previous FVIII/vWF concentrate requirements, response to therapy, body weight, and reason for usage.

Table 5: Guidelines for Dosage during the efficacy component

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

b.w. = body weight; FVIII = factor VIII; FVIII:C = factor VIII:coagulant activity; IU = International Unit; NSB = non-surgical bleeding; VWF = Von Willebrand factor; VWF:RCo = Von Willebrand factor:Ristocetin Cofactor.

Objectives

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

The secondary objectives included the assessment of the safety of Voncento used both as on-demand therapy to treat NSB events and as prophylactic therapy and the assessment of the haemostatic efficacy of Voncento for subjects who undergo surgical procedures during the study period.

Outcomes/endpoints

No particular efficacy variable was defined as primary for this study.

Efficacy measurements

The clinical efficacy parameters assessed in the study were haemostasis assessment (overall every 3 months by the investigator and for each non-surgical bleed (NSB) and surgical event by the investigator and subject), study product usage, blood product transfusion requirements, and surgeon's assessment of blood loss during a surgical procedure.

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.

Haemostasis assessment

Overall clinical assessments of haemostatic efficacy for both prophylaxis and on demand treatment were based on a 4-point Efficacy Grading Scale (Table 6) by both the subject and the investigator throughout the efficacy component of the study.

Table 6: 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

To complete the guideline requirements (November 2005 CHMP guideline, CPMP/BPWG/220/02) 12 subjects with VWD to take part in a PK study, 6 of whom should have Type 3 VWD were required. In addition, data on at least 10 NSB events, of which 5 were to be major mucosal NSB events, were required. Subjects who required prophylaxis therapy with a VWF product were also required; 2-5 subjects fulfilling this requirement were planned to be enrolled.

Hence, 25 subjects were expected to enrol into the efficacy component to ensure

• 2-5 subjects receiving a set prophylaxis therapy with Voncento for a period of 12 months, and

• a minimum of 10 evaluable NSB events, including at least 5 events classified as major mucosal NSB events. An evaluable NSB event was an event that required treatment with Voncento and had undergone at least 1 haemostatic efficacy assessment by the investigator.

This estimate of 25 subjects included 16 VWD subjects to be enrolled in the PK component (10 of these diagnosed with Type 3 VWD) to ensure ≥12 evaluable subjects who complete the initial PK sampling and 6 subjects with Type 3 VWD who complete the initial and repeat PK sampling.

Randomisation

N/A.

Blinding (masking)

This was an open-label study.

Statistical methods

An interim analysis was performed after the completion of Part 1 with a PK Study Report being prepared and released based on the analysis of the data from this component of the study. No formal statistical tests were performed.

Two-sided 90% confidence intervals (CIs) were computed for PK analyses only. All analyses were considered exploratory, and thus no adjustments for multiplicity were applied.

In general descriptive statistics were used to summarise efficacy data by treatment arm and overall. Missing data were not replaced and therefore summaries were based on the observed data.

The statistical analysis was based on the following analysis populations:

• Safety population: all subjects who received at least 1 dose of study product.

• PK population: all subjects who received at least 1 dose of study product and had at least 5 analyzable samples (including the pre-infusion sample) to evaluate the PK profile of Voncento.

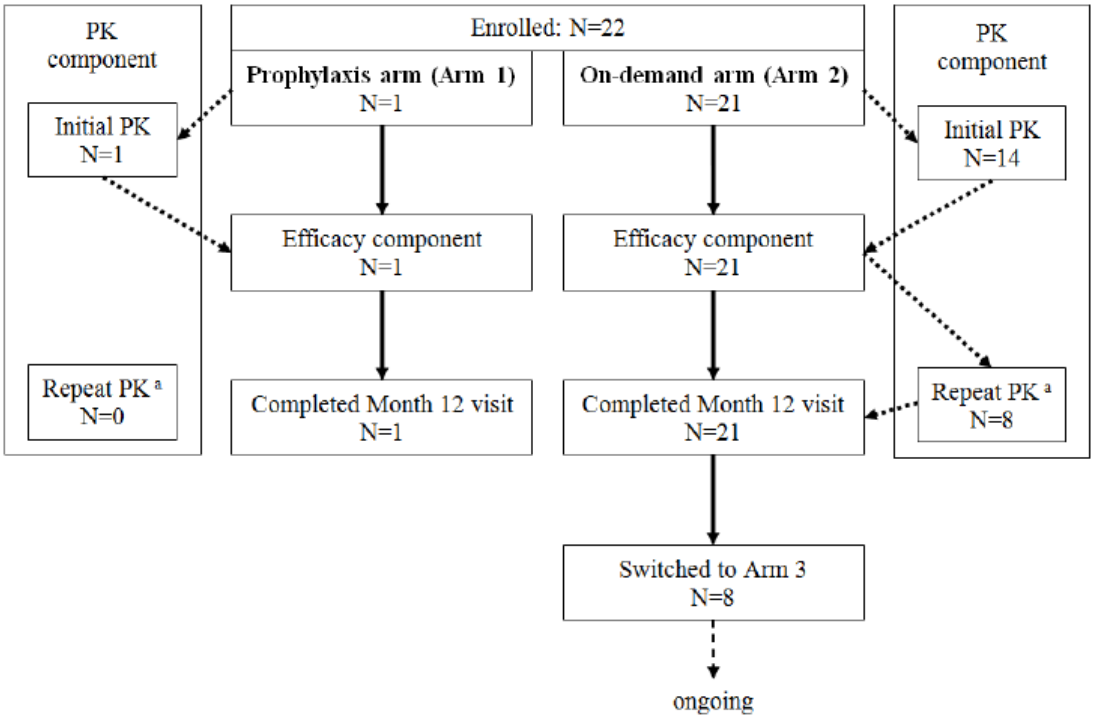
• Efficacy population: all subjects who participated in the efficacy component of the study (either for set prophylaxis or have experienced at least 1 NSB event) and who received at least 1 dose of study product and who have at least 1 post-baseline haemostasis assessment by an investigator.

• PP population: all subjects of the efficacy population who completed the study without any major protocol deviations and who attended all required study visits.

Results

Participant flow

Figure 3: Subject disposition (study CSLCT-BIO- 08-54)



[a] for PK subjects with Type 3 VWD only.

Recruitment

A total of 22 subjects received study drug in 6 centres in Brazil, Bulgaria, Poland (2), Russia and Ukraine. The first subject was enrolled on 30 June 2009 and the last subject completed their 12 month visit on 6 March 2011.

Arm 3 which includes 8 subjects on regular long term prophylaxis was still ongoing at the time of the submission.

Conduct of the study

Three substantial amendments and 1 non-substantial amendment were issued after the study protocol had been finalised on 10 October 2008. Main changes from these amendments are outlined below:

Substantial amendment 1 was issued on 15 December 2008, before the enrolment of any subjects, and included the following main changes; All subjects had their VWD phenotype confirmed at the screening visit; the duration of the screening period was increased to up to 21 days to allow sufficient processing time for the phenotype assessment; reduced blood volumes for adolescents were inserted; introduction of a Data Safety Monitoring Board.

Substantial amendment 2 was issued on 23 April 2009, before the enrolment of any subjects, and included the following main changes: reduction in the volume of blood taken for both adults and adolescents (the same volumes required for adults and adolescents); removal of Human Immunodeficiency Virus testing at screening; modification of the requirements for Hepatitis C testing at screening; the duration of the screening period was increased to up to 28 days to allow sufficient processing time for the phenotype assessment; confirmation that a urine pregnancy test rather than a serum pregnancy test was to be performed in females of childbearing potential at screening; bicarbonate

testing was deleted from Biochemistry determinations; clarification regarding Hepatitis A and Hepatitis B eligibility testing at screening and pre-dose vaccination requirements.

Substantial amendment 3 was issued on 15 December 2009. At that time, 13 subjects had already been enrolled into the study. The further conduct of the study for already enrolled subjects was not affected by this amendment. The following main changes were included: adjustment of wash-out period prior to the screening visit; adjustment of safety assessments with regard to suspected inhibitor formation.

Non-substantial amendment 4 was issued on 29 July 2010. At that time, 21 subjects had already been enrolled into the study; however, the further conduct of the study was not affected by this amendment. The following main changes were included: subjects were allowed to start with prophylaxis treatment regardless of the previous regimen; criteria for the interim analysis were adapted.

Baseline data

Baseline demographics and baseline disease characteristics are summarised in tables 7 and 8 respectively.

Table 7: Baseline demographics

Variable	Safety population N=22	PK population N=15
Sex, n (%)		
Male	10 (45.5)	7 (46.7)
Female	12 (54.5)	8 (53.3)
Ethnic origin, n (%)		
Caucasian	22 (100.0)	15 (100.0)
Age [years]		
Mean (SD)	33.6 (15.2)	32.5 (11.3)
Median (range)	30.5 (15 - 68)	33.0 (15 - 50)
<18 years, n (%)	3 (13.6)	1 (6.7)
≥18 years, n (%)	19 (86.4)	14 (93.3)
Weight [kg]		
Mean (SD)	72.64 (15.03)	74.94 (14.22)
Median (range)	71.00 (51.5 - 98.5)	73.0 (58.0 - 99.0)
Height [cm]		
Mean (SD)	168.7 (7.9)	169.4 (8.4)
Median (range)	168.0 (155 - 182)	168.0 (155 - 182)

n = number of subjects with characteristic; N = total number of subjects; PK = pharmacokinetics; SD = standard deviation.

Table 8: Baseline disease characteristics

Variable	Safety population N=22	PK population N=15
VWD Type, n (%)		
Type 1	5 (22.7)	4 (26.7)
Type 2A	4 (18.2)	3 (20.0)
Type 3	13 (59.1)	8 (53.3)
Years since first VWD diagnosis		
Mean (SD)	22.9 (14.8)	21.7 (9.1)
Median (range)	17.5 (3 - 67)	20.1 (3 - 36)
Number of bleeding events per subject during the past 12 months		
Mean (SD)	3.8 (4.0)	2.0 (1.3)
Median (range)	2.0 (1 - 15)	2.0 (1 - 5)
Classification of previous bleeding events, n (%)[a]		
Major	12 (14.5)	7 (23.3)
Minor	50 (60.2)	23 (76.7)
Response to VWF treatment for previous bleeding events, n (%)[a]		
Excellent	4 (4.8)	4 (13.3)
Good	36 (43.4)	18 (60.0)
Moderate	10 (12.0)	8 (26.7)
None	0	0

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

[a] Percentages are based on the number of bleeding events in the 12 months prior to study entry; percentages do not add up to 100% due to missing information for some bleeding events.

Numbers analysed

A total of 22 subjects, including 3 adolescents, were treated in the study and thus comprise the safety population.

Twenty-one subjects were not eligible for the prophylaxis arm (Arm 1, n=1) but required a VWF product for the treatment of NSB events and thus comprise the on-demand arm (Arm 2) of this study. One subject in Arm 2 did not have an evaluable NSB event and was therefore excluded from the efficacy population. One further subject was excluded from the PP population (n=20) due to a major protocol violation. Efficacy results in the PP population were similar to those in the efficacy population and unless stated otherwise are not specifically mentioned in the following section.

Since there was only 1 subject in Arm 1, the prophylaxis arm, efficacy results are summarised in the following tables for both treatment arms combined, ie, for the overall efficacy population (N=21). Thus the total number of patients evaluated for efficacy in the treatment of bleeding events was 21.

- **Outcomes and estimation**

3-monthly assessment of haemostatic efficacy

The investigator's 3-monthly assessment of haemostatic efficacy is summarised in Table 9.

For each 3-month interval the subject's haemostatic efficacy was assessed as either excellent or good, with 1 exception each at Month 6 and Month 12, where 1 subject's haemostatic efficacy was assessed as moderate. These 2 assessments of moderate haemostatic efficacy were both related to the subject in the prophylaxis arm; the only other available haemostatic efficacy assessment for this subject was "excellent" at Month 9. The subject had 2 NSB events each during the first, second, and fourth 3-month

period; however, as the subject did not alter the prophylactic treatment scheme, none of these events were treated with Voncento. These NSB events were not assessed for haemostatic efficacy.

Table 9: Investigator's 3-monthly haemostatic efficacy assessment (efficacy population)

Month	Number of assessed subjects	Number (%) of subjects [a]			
		Excellent	Good	Moderate	None
Month 3	17	15 (88.2)	2 (11.8)	0	0
Month 6	20	13 (65.0)	6 (30.0)	1 (5.0)	0
Month 9	17	14 (82.4)	3 (17.6)	0	0
Month 12	19	15 (78.9)	3 (15.8)	1 (5.3)	0

[a] includes subjects who did not have any bleeding events during the study.

Non-surgical bleeding events

A total of 538 NSB events were reported during the study. The median number of NSB events per subject was 19 and ranged from 2 to 82; 534 (99.3%) of NSB events were spontaneous, 527 (98.0%) were minor, 422 (78.4%) were mucosal, and 380 (70.6%) were treated at home.

Seven subjects had a total of 132 NSB events that did not require treatment with Voncento and which were therefore considered not evaluable and consequently not assessed for haemostatic efficacy.

In addition to the above mentioned 132 non-treated NSB events, 1 minor mucosal NSB event experienced at home by one subject and for which 2 Voncento infusions were administered was also not assessed by the investigator for haemostatic efficacy.

Of the 538 reported NSB events, haemostatic efficacy was assessed for 405 events treated with Voncento (Table 10), which all occurred in the on-demand arm (Arm 2). Subject's assessment of haemostatic efficacy per day of bleeding event is shown in table 11.

Table 10: Investigator's assessment of haemostatic efficacy per bleeding event (efficacy population)

Bleeding type	Number of NSB events [a]	Number (%) of NSB events			
		Excellent	Good	Moderate	None
All NSB events	405	371 (91.6)	27 (6.7)	7 (1.7)	0
Spontaneous	401	367 (91.5)	27 (6.7)	7 (1.7)	0
Trauma	3	3 (100)	0	0	0
Post-surgery	1	1 (100)	0	0	0
Major [b]	8	2 (25.0)	0	6 (75.0)	0
Minor	397	369 (92.9)	27 (6.8)	1 (0.3)	0
Joint	101	99 (98.0)	2 (2.0)	0	0
Mucosal	289	257 (88.9)	25 (8.7)	7 (2.4)	0
Muscle	17	17 (100)	0	0	0

NSB = non-surgical bleeding.
[a] NSB events treated with Biostate and with a haemostatic efficacy assessment.
[b] Includes 7 mucosal events.

Table 11: Subject's assessment of haemostatic efficacy per day of bleeding event (efficacy population)

	Number (%) of bleeding days

Day	Number of bleeding days	Excellent	Good	Moderate	None
All days	602	476 (79.1)	104 (17.3)	21 (3.5)	1
Day 1	392	334 (85.2)	44 (11.2)	14 (3.6)	0
Day 2	77	47 (61.0)	25 (32.5)	4 (5.2)	1
Day 3	63	46 (73.0)	16 (25.4)	1 (1.6)	0
Day 4	52	41 (78.8)	10 (19.2)	1 (1.9)	0
Day 5	18	8 (44.4)	9 (50.0)	1 (5.6)	0

NSB = non-surgical bleeding.

Major non-surgical bleeding events

In the efficacy population, 5 subjects had 11 NSB events that were considered as major by the Investigator. All events were spontaneous and mucosal with the exception of 1 trauma bleeding that affected the muscle. None of the 3 major NSB events of one subject (Arm 1) were treated on-demand with Voncento; these events were therefore not evaluated for haemostatic efficacy.

The overall haemostatic efficacy for the 8 evaluable major NSB events was assessed by the Investigator as excellent in 2 cases and as moderate in the remaining 6 cases. These 6 events were all major mucosal/uterine NSB events experienced by 2 subjects; for 4 of these events, the investigator assessed the haemostatic efficacy as good on at least 1 bleeding day. The duration of the major NSB events varied from 8.2 h to more than 12 days. One subject who had 3 major NSB events was excluded from the PP population due to a time window violation.

Surgical events

Four subjects, including 2 adolescent subjects underwent 1 surgery each during the study prior to the date of database lock. All 4 surgical events were minor and included 3 cases of tooth extraction and a biopsy of the cervix. The investigator's assessment of haemostatic efficacy at discharge from the hospital was available for 3 surgical events and was assessed as excellent for 2 surgical events and as good for 1 event. For the event with missing haemostatic efficacy assessment at discharge, the Investigator rated the post-surgery haemostatic efficacy as excellent.

Usage of the study product

Subjects in the on-demand arm (Arm 2) had a median number of 19.5 infusions (range: 3-92) at a median Voncento dose of 39.0 VWF:RCo IU/kg (range: 15-53 IU/kg). Results were similar when only considering infusions given for a NSB event. The one subject included in the prophylaxis arm (Arm 1) of the study had 142 infusions with 20.0 VWF:RCo IU/kg Voncento per infusion administered every 2-3 days. The vast majority of NSB events required 1 single infusion of Voncento; 8 subjects experienced a total of 25 NSB events that required more than 1 infusion of Voncento.

Blood loss during surgical events

The blood loss during the 4 surgical events in the efficacy population was assessed by the investigator or surgeon as less than expected (in a subject without a bleeding disorder) for 1 surgical event and equivalent to the expected loss for 3 surgical events.

Blood product transfusions

One subject in the efficacy population required blood product transfusion: 600 mL of packed RBCs each for 2 cases of major uterine bleeding that occurred about 2 months apart. About 1 month after the second of these events, the subject experienced a third major uterine NSB event that did not require any blood product transfusion.

Ancillary analyses

The efficacy data of the 3 adolescent subjects (2 aged 15 and one 16 years) have been submitted by the applicant. All were on-demand treatment. The 3 adolescent subjects in the study received 12 infusions of Voncento with an average dose of 32.9 IU/kg, 21 infusions with an average of 41.8 IU/kg, and 4 infusions with an average dose of 27.3 IU/kg. 2 Adolescents required minor surgery during the course of the study. Haemostatic efficacy was assessed as either good or excellent for all NSB and surgical events for which Voncento was administered.

- **Study CSLCTBIO- 07-47 (Haemophilia A indication)**

Study CSLCTBIO- 07-47 was a phase II, multicentre, double-blinded, randomised, cross-over study to evaluate the efficacy, safety, and pharmacokinetics of Voncento in subjects with haemophilia A.

Methods

Study Participants

Main inclusion criteria:

- Male of at least 12 years
- Subjects with haemophilia A and FVIII levels of ≤1% in the absence of factor replacement according to their medical history
- Evidence of vaccination against hepatitis A and B (or presence of antibodies against hepatitis A and B due to either a previous infection or prior immunisation) within 10 years prior to Day 1 as documented in their medical notes
- At least 150 prior exposure days to a FVIII replacement product confirmed by their treating physician(s)

Main exclusion criteria:

For participation in the PK part

- Bleeding
- Body weight >100 kg

The most relevant exclusion criteria for all subjects at Day 1 were

- Subjects who had received an infusion of any FVIII product, cryoprecipitate, whole blood, plasma, or desmopressin acetate in the 4 days prior to Day 1
- Known history of FVIII inhibitors, or had a FVIII inhibitor level of ≥0.6 Bethesda Units (BU) at screening
- Treatment with aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) within 7 days of administration of study drug
- CD4 lymphocytes <200/µL (in the medical history and/or at screening if available results were older than 1 year). Subjects that were human immunodeficiency virus (HIV)-1 positive may have been considered for the study if viral load ≤200 particles/µL at screening, and all other eligibility criteria were met
- Impaired liver function, ie, bilirubin >1.5 × upper limit of normal (ULN) and/or aspartate transaminase (AST)/alanine transaminase (ALT) >2.5 × ULN (referring to limits of the laboratory that performed the determination) at screening

Treatments

The study consisted of 4 periods:

- Screening period of up to 14 days.
- Part 1 of the study was a Phase II, multicentre, double-blind, randomised, cross-over study to evaluate the PK and safety of Voncento SP compared to Voncento RP.
- Part 2 of up to 6 months of Voncento SP therapy as required, for a minimum of 50 exposure days (efficacy component, all subjects). If the 50 exposure days did not occur in the predicted 6-month period, the subject was allowed to continue in the study until he required the administration of Voncento on at least 50 separate occasions/events.
- Part 3 of up to 8 days (repeat PK assessment of the PK component, PK subjects only) consisted of a single dose of Voncento SP on Day 180 with PK samples collected on Days 180, 181, and 182. A minimum of 4 days was required from the last dose of Voncento SP prior to receiving the single dose of Voncento SP for the purpose of Part 3 PK assessment.

A final follow-up safety visit occurred on Day 187, which also constituted the final visit, if the subject had a minimum of 50 exposure days. Otherwise the final visit was to occur within 7 days after the last dose of Voncento SP. The individual duration for the total study was at least 32 weeks for subjects participating in the PK and efficacy components and at least 29 weeks for subjects participating in the efficacy component only.

In the PK component of the study subjects received 50 IU/kg FVIII of Voncento RP or Voncento SP based on the subject's body weight.

For each subject in the efficacy component (Part 2) of the study, the frequency and dose (loading and maintenance) of Voncento SP was determined by the Investigator. The dose was based on the subject's clinical condition, previous FVIII concentrate requirements, response to therapy, body weight, and reason for usage (on-demand treatment for a haemorrhage or surgery or as prophylaxis) during the 6-month efficacy period (for a minimum of 50 exposure days).

Prophylaxis was intended for subjects who had been on a set prophylaxis regimen with a FVIII product at the time of study entry or for subjects who were eligible to receive prophylaxis treatment based on the severity of their disease.

Objectives

The primary objectives of the study were the assessment of the efficacy of Voncento SP in subjects with haemophilia A and the assessment of the comparability of the PK of Voncento RP and Voncento SP in subjects with haemophilia A.

The secondary objective was to assess the safety of Voncento SP in subjects with haemophilia A.

Outcomes/endpoints

The clinical efficacy parameters assessed in the study were study product usage, haemostasis assessment (by the subject and Investigator), blood product transfusion requirements, and surgeon's assessment of blood loss during a surgical procedure.

Study product usage

The following information was collected on the administration of both Voncento RP and SP, for each dose that the subject received: reason for use; dose of Voncento (FVIII:C [IU/kg]); total number of vials used;

batch number(s) of each vial; infusion start and stop times; total volume infused; number of infusions per day (frequency); total days of treatment required.

Haemostasis assessment

Overall clinical assessments of haemostatic efficacy were based on the 4-point Efficacy Grading Scale (presented in main study of VWD indication) by both the subject and the Investigator throughout the efficacy (Part 2) component of the study.

Blood product transfusion requirements

The type of blood product, and the number of units required by a subject during the study period (screening to final visit) were recorded. This included any infusions of whole blood, packed RBCs, and platelets.

Assessment of blood loss during surgery

In the case of any surgical procedures, the surgical team provided an assessment at the time of the procedure of the extent of blood loss for each specific surgical procedure performed on a subject. The blood loss was compared to the expected blood loss from a subject without a bleeding disorder undergoing the same procedure and judged to be “less”, “equivalent”, or “more”.

Sample size

The number of subjects is based on the requirements for bioequivalence studies in conjunction with the draft *CPMP Note for Guidance on the Clinical Investigation of Human Plasma-Derived Factor VIII and Factor IX Products (July 2007).*

It was anticipated that approximately 80 adults and adolescents (≥12 years) who have been diagnosed with haemophilia A with FVIII levels ≤1% would be recruited into this study to obtain PK data on a minimum of 12 subjects, and efficacy and safety data on a minimum of 65 subjects.

Randomisation

During Part 1 of the study subjects were randomised on Day 1 in a 1:1 ratio to receive:

• Voncento RP on Day 1 and Voncento SP on Day 8, or

• Voncento SP on Day 1 and Voncento RP on Day 8.

Blinding (masking)

Blinding was only applicable for Part 1 of the study.

Statistical methods

The following populations were defined for the analysis:

- Efficacy population: all subjects who received at least 1 dose of Voncento SP during the efficacy component (Part 2) and had at least 1 post-baseline haemostasis assessment by the Investigator;
- Per-protocol (PP) population: all subjects of the efficacy population who attended all required study visits, completed the study, and were without any major protocol violations;
- Safety population: all subjects who received at least 1 dose of study drug (either Voncento SP or RP). Subjects were included in the analysis according to the treatments actually received.

No formal statistical tests were performed. P-values should be interpreted in an exploratory manner. Two-sided 90% confidence intervals (CIs) were computed for PK analyses only. All analyses were considered exploratory, and thus no adjustments for multiplicity were applied.

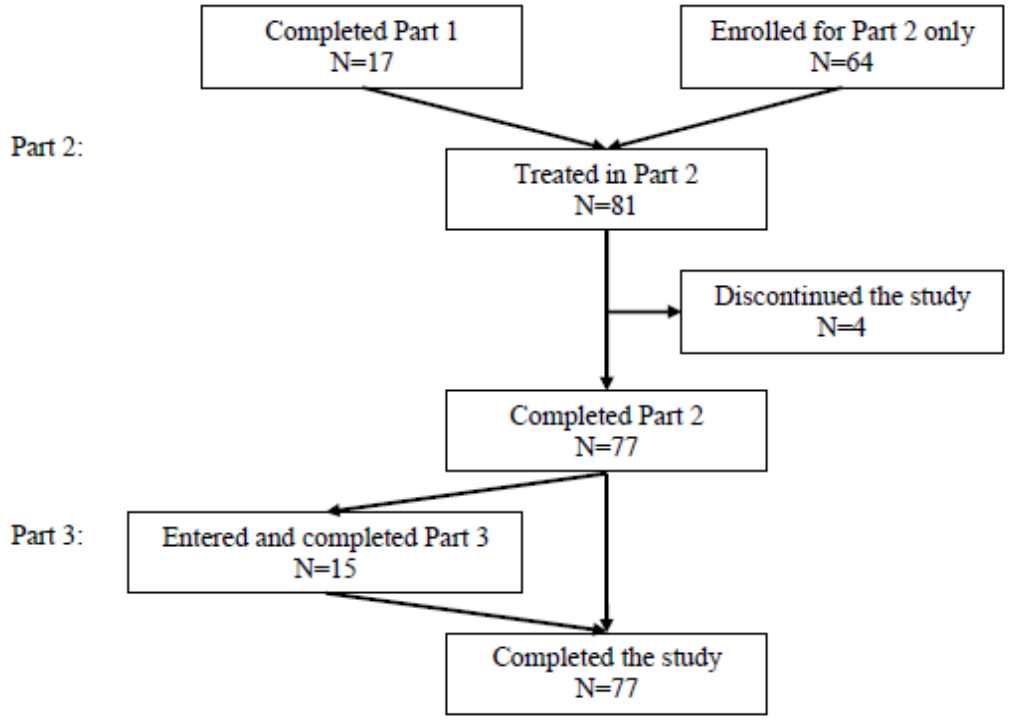
Missing data were not replaced; summaries were based on observed data.

The following subgroups of subjects were considered for selected analyses:

- On-demand subgroup: All Voncento infusions in Part 2 were given due to bleeding or surgical events, but none for prophylaxis or prevention.
- Prophylaxis subgroup: ≥90% of the Voncento infusions in Part 2 (excluding the first infusion) were applied ≤3 days after the previous Voncento infusion, excluding subjects of the on-demand subgroup.
- Prevention subgroup: <90% of the Voncento infusions in Part 2 (excluding the first infusion) were applied ≤3 days after the previous Voncento infusion, excluding subjects of the on-demand subgroup.
- ***Results***

Participant flow

Figure 4: Patient disposition for Parts 2 and 3



Recruitment

A total of 81 patients received study drug in 14 centres in Bulgaria (3) Republic of Macedonia (1), Poland (7), and Russia (3).

The first subject was enrolled on 31 March 2009 and the last completed on 15 October 2010.

Conduct of the study

Three general substantial amendments and 2 country-specific amendments for Russia were issued after the study protocol had been finalised on 10 September 2008. Main changes from these amendments are outlined below.

- Amendment 1 was issued on 21 January 2009, before the enrolment of any subjects, and included the following main changes: increase of the duration of the screening period to up to 14 days to allow sufficient processing time for the screening assessment; reduced blood volumes for children were inserted; introduction of the Independent Data Monitoring Committee (IDMC); definition of major bleeding events was revised; FVIII level, haematology, and biochemistry determinations prior to major bleeding events or surgical procedures, respectively, were deleted.
- Amendment 2 was issued on 29 April 2009, before the enrolment of any subjects, and included the following main changes: change of the exclusion criteria to allow the admission of subjects with a positive hepatitis C viral load but to exclude subjects with an active hepatitis C; bicarbonate testing was deleted from biochemistry determinations; inconsistencies with regard to the start of the reporting period of AEs were resolved.
- Amendment 3 was issued on 04 November 2009. At that time, 3 subjects included in the analyses for this report had been enrolled. The further conduct of the study for already enrolled subjects was not affected by this amendment. The following main changes were included: change of laboratory parameters at screening to perform HIV viral load testing only if subjects were HIV antibody positive; increase of the number of enrolled subjects to approximately 80. This change in sample size was made in order to collect more efficacy data; the PK component and thus the sample size estimation was not affected by this change; increase of the number of evaluable subjects to at least 65; Specification of “prevention of bleedings” within the on-demand treatment regimen.

Country-specific amendment 1 for Russia was issued on 24 July 2008 to change the minimum age of subjects to be included in Russia to 18 years and amendment 2 was issued on 08 July 2009 to add that the HIV viral load was only to be determined if the subject was HIV positive.

Baseline data

Baseline demographics and baseline disease characteristics are summarised in tables 12 and 13 respectively.

Table 12: Baseline demographics

Variable	Safety/Efficacy population N=81	PP population N=68	PK safety population N=17
Age [years]			
Mean (SD)	33.1 (12.8)	32.7 (13.0)	36.5 (12.7)
Median (range)	32.0 (13 - 68)	30.5 (13 - 68)	37.0 (18 - 57)
<18 years, n (%)	3 (3.7)	3 (4.4)	0
≥18 years, n (%)	78 (96.3)	65 (95.6)	17 (100.0)
Ethnic origin, n (%)			
Caucasian	81 (100.0)	68 (100.0)	17 (100.0)
Weight [kg]			
Mean (SD)	74.5 (16.44)	73.9 (16.00)	75.16 (15.54)
Median (range)	72.0 (50 - 130)	70.8 (50 - 125)	74.0 (50.0 - 98.0)
Height [cm]			
Mean (SD)	174.9 (8.5)	174.9 (8.4)	176.2 (5.8)
Median (range)	175.0 (152 - 194)	175.0 (152 - 190)	176.0 (165 - 190)

n = number of subjects with characteristic; N = total number of subjects; PK = pharmacokinetic; PP = per-protocol; SD = standard deviation.

Note: All subjects were male.

Table 13: Haemophilia History

Variable	Safety/Efficacy population N=81	PP population N=68	PK safety population N=17
Years since first haemophilia A diagnosis			
Number of subjects with data	79	66	17
Mean (SD)	31.5 (11.5)	30.9 (11.6)	35.8 (12.5)
Median (range)	29.9 (13 - 61)	29.4 (13 - 61)	36.5 (17 - 57)
Years since first severe haemophilia A diagnosis			
Number of subjects with data	72	61	12
Mean (SD)	21.9 (15.9)	21.3 (15.9)	30.4 (9.9)
Median (range)	22.4 (0 - 61)	22.2 (0 - 61)	30.1 (17 - 46)
Years since last FVIII level <1%			
Number of subjects with data	54	48	10
Mean (SD)	4.2 (7.0)	4.4 (7.3)	5.9 (8.4)
Median (range)	1.2 (0 - 34)	1.3 (0 - 34)	1.4 (0 - 24)
Haemarthrosis of joints, n (%)	75 (92.6)	62 (91.2)	15 (100)
Number of bleeding events during the past 12 months			
Number of subjects with data	54	49	9
Mean (SD)	42.7 (29.3)	41.6 (28.5)	26.9 (35.0)
Median (range)	40.0 (1 - 116)	39.0 (18 - 116)	12.0 (3 - 111)

FVIII = Factor VIII; n = number of subjects with characteristic; N = total number of subjects; PK = pharmacokinetic; PP = per-protocol; RP - SP = Day 1: Biostate RP, Day 8: Biostate SP; SD = standard deviation.

Numbers analysed

The statistical analysis was based on the following analysis populations:

- Safety population of 81 patients (100%): all subjects who received at least 1 dose of study drug (either Voncento SP or RP).
- Safety population for Part 1 (17 patients): all subjects of the safety population, who participated in the PK component of the study.
- Efficacy population of 81 patients (100%): all subjects who received at least 1 dose of Voncento SP during the efficacy component (Part 2) and had at least 1 post-baseline haemostasis assessment by the Investigator.
- Per-protocol (PP) population of 68 patients (84%).

Outcomes and estimation

Haemostatic efficacy

The Investigator's assessment of haemostatic efficacy is shown by month in Table 14. Results in the PP population were comparable (data not shown).

Table 14: Investigator's monthly haemostatic efficacy assessment (efficacy population)

Month	Number of subjects	Number (%) of subjects [a]			
		Excellent	Good	Moderate	None
Month 1	81	58 (71.6)	21 (25.9)	2 (2.5)	0
Month 2	81	64 (79.0)	17 (21.0)	0	0
Month 3	80	63 (78.8)	16 (20.0)	1 (1.3)	0
Month 4	80	64 (80.0)	16 (20.0)	0	0
Month 5	79	68 (86.1)	11 (13.9)	0	0
Month 6	78	66 (84.6)	12 (15.4)	0	0
Month 7	20	16 (80.0)	4 (20.0)	0	0
Month 8	15	13 (86.7)	2 (13.3)	0	0
Month 9	9	8 (88.9)	1 (11.1)	0	0
Month 10	7	5 (71.4)	2 (28.6)	0	0

[a] includes subjects who did not have any bleeding events during the study.

Haemostatic efficacy assessment of bleeding events

A total of 667 bleeding events were reported during the study. The number of bleeding events are summarised in Table 15, overall and by bleeding type. Eleven subjects in the prophylaxis subgroup and 6 subjects in the prevention subgroup had no bleeding events during the study. The median number of bleeds per month in the first month was 0 in the prophylaxis sub-group (range 0 to 5) and 1 in the prevention sub-group (range 0 to 8) and values were almost the same in the following months.

Table 15: Number of bleeding events per subject (efficacy population)

	N	Mean	SD	Min	Median	Max
All subjects [a]						
Any bleeding event	81	8.2	9.4	0	5.0	44
Prophylaxis subgroup	29	3.5	4.7	0	1.0	18
Prevention subgroup	51	10.7	10.3	0	9.0	44
On-demand subgroup	1	22	-	22	22	22
Subjects with at least 1 bleeding event						
Any bleeding event	64	10.4	9.4	1	9.0	44
Bleeding type						
Spontaneous	58	9.8	9.3	1	7.5	42
Trauma	34	2.8	2.6	1	2.0	12
Post-surgery [b]	4	1.3	0.5	1	1.0	2
Major	15	2.7	3.2	1	1.0	11
Minor	63	10.0	8.8	1	9.0	42
Joint	61	9.0	8.1	1	8.0	41
Mucosal	16	2.1	2.0	1	1.5	8
Muscle	33	2.6	2.9	1	2.0	15

Min = minimum; Max = maximum; N = number of subjects; SD = standard deviation.
[a] Includes 17 subjects who did not have a bleeding event during the study.
[b] Post-operative bleeding event; surgical events are discussed below.

A descriptive analysis of the number of bleeding events per subject by categories of mean time between Voncento administrations (<3, 3-<4, ≥4 days) indicated that the more time there was between Voncento administrations the more bleeding events occurred on average (Table 16).

Table 16. Summary of number of bleedings by mean time between Voncento administrations Efficacy and PP population

	N	MEAN	SD	MIN	P25	MEDIAN	P75	MAX
Efficacy population (N=81)								
All bleedings	81	8.2	9.4	0	1.0	5.0	12.0	44
Mean time between Biostate administrations								
<3 days	36	6.8	9.9	0	0.0	2.5	10.5	44
3-<4 days	26	7.0	8.4	0	1.0	3.0	11.0	31
>=4 days	19	12.7	8.6	3	7.0	12.0	15.0	42

	N	MEAN	SD	MIN	P25	MEDIAN	P75	MAX
PP population (N=68)								
All bleedings	68	8.3	9.8	0	1.0	4.5	12.5	44
Mean time between Biostate administrations								
<3 days	32	6.0	9.7	0	0.0	1.5	8.0	44
3-<4 days	22	7.6	8.8	0	2.0	3.5	11.0	31
>=4 days	14	14.7	9.0	5	10.0	12.5	18.0	42

Haemostatic efficacy was assessed for 656 of the 667 reported bleeding events (Table 17).

Table 17: Investigator's assessment of haemostatic efficacy per bleeding event (efficacy population)

Bleeding type	Number of bleeding events [a]	Number (%) of bleeding events			
		Excellent	Good	Moderate	None
All bleeding events	656	396 (60.4)	236 (36.0)	23 (3.5)	1 (0.2)
Spontaneous	561	337 (60.1)	204 (36.4)	19 (3.4)	1 (0.2)
Trauma	90	56 (62.2)	31 (34.4)	3 (3.3)	0
Post-surgery [b]	5	3 (60.0)	1 (20.0)	1 (20.0)	0
Major	40	11 (27.5)	22 (55.0)	7 (17.5)	0
Minor	616	385 (62.5)	214 (34.7)	16 (2.6)	1 (0.2)
Joint	543	323 (59.5)	203 (37.4)	16 (2.9)	1 (0.2)
Mucosal	34	18 (52.9)	14 (41.2)	2 (5.9)	0
Muscle	81	55 (67.9)	21 (25.9)	5 (6.2)	0

[a] Bleeding events with a haemostatic efficacy assessment.
[b] Post-operative bleeding event; surgical events are discussed below.

Haemostatic efficacy results for the prophylaxis and prevention are summarised in table 18.

Table 18: Investigator's assessment of haemostatic efficacy per bleeding event, by prophylaxis and prevention subgroups (efficacy population)

Subgroup		Number (%) of bleeding events			
Bleeding type	Number of bleeding events [a]	Excellent	Good	Moderate	None
Prophylaxis (N=29)					
All bleeding events	97	64 (66.0)	31 (32.0)	2 (2.1)	0
Spontaneous	66	42 (63.6)	23 (34.8)	1 (1.5)	0
Trauma	29	21 (72.4)	8 (27.6)	0	0
Post-surgery	2	1 (50.0)	0	1 (50.0)	0
Major	4	0	3 (75.0)	1 (25.0)	0
Minor	93	64 (68.8)	28 (30.1)	1 (1.1)	0
Joint	81	55 (67.9)	25 (30.9)	1 (1.2)	0
Mucosal	6	2 (33.3)	3 (50.0)	1 (16.7)	0
Muscle	11	7 (63.6)	4 (36.4)	0	0
Prevention (N=51)					
All bleeding events	537	316 (58.8)	199 (37.1)	21 (3.9)	1 (0.2)
Spontaneous	473	279 (59.0)	175 (37.0)	18 (3.8)	1 (0.2)
Trauma	61	35 (57.4)	23 (37.7)	3 (4.9)	0
Post-surgery	3	2 (66.7)	1 (33.3)	0	0
Major	25	6 (24.0)	13 (52.0)	6 (24.0)	0
Minor	512	310 (60.5)	186 (36.3)	15 (2.9)	1 (0.2)
Joint	455	265 (58.2)	174 (38.2)	15 (3.3)	1 (0.2)
Mucosal	28	16 (57.1)	11 (39.3)	1 (3.6)	0
Muscle	55	35 (63.6)	15 (27.3)	5 (9.1)	0

[a] Bleeding events with a haemostatic efficacy assessment; includes 6 events in the prophylaxis subgroup (4 excellent, 2 good) and 6 events in the prevention subgroup (5 excellent, 1 good) that were reported as not requiring any Biostate infusion.

Based on the subject's assessment of haemostatic efficacy, for 87.9% of bleeding days the haemostatic efficacy was assessed by the subject as either excellent or good, and for 11.0% as moderate; for 10

bleeding days (1.1%), no haemostatic efficacy was seen according to the subject's assessment. Only 38 bleeding events lasted more than 2 days. Results in the PP population were comparable (data not shown).

Haemostatic efficacy assessment of surgical events

A total of 37 surgical events, 12 major and 25 minor, occurred during the study in 20 subjects of the efficacy population. A haemostatic efficacy assessment at discharge was provided by the Investigator for 20 surgical events: 10 major in 10 subjects and 10 minor in 3 subjects. At discharge, the Investigator assessed the haemostatic efficacy for 2 of the major surgical events as good and for the remaining major and minor surgical events as excellent.

Table 19: Surgical events: Assessment of haemostatic efficacy and blood loss per event (efficacy population)

Assessment Surgical event type	Number of surgical events	Number (%) of surgical events			
Haemostatic efficacy		**Excellent**	**Good**	**Moderate**	**None**
Post-surgery assessment					
All surgical events	15 [a]	12 (80.0)	3 (20.0)	0	0
Major	2	2 (100.0)	0	0	0
Minor	13	10 (76.9)	3 (23.1)	0	0
Assessment at discharge					
All surgical events	20 [a]	18 (90.0)	2 (10.0)	0	0
Major	10	8 (80.0)	2 (20.0)	0	0
Minor	10	10 (100.0)	0	0	0
Blood loss		**Less**	**Equivalent**	**More**	
All surgical events	37	15 (40.5)	21 (56.8)	1 (2.7)	
Major	12	6 (50.0)	5 (41.7)	1 (8.3)	
Minor	25	9 (36.0)	16 (64.0)	0	

[a] Surgical events with a haemostatic efficacy assessment available.

Results in the PP population were similar (data not shown).

Blood loss during surgical events

The blood loss during the 37 surgical events in the efficacy population (Table 19) was assessed as more than expected for 1 surgical event (2.7%). This latter surgical event was reported for one subject who underwent a major knee surgery (total replacement) which required 1 Voncento infusion of 50 IU/kg prior to or during surgery and 18 post-surgery infusions of a total of 885 IU/kg Voncento; the subject also required 4 transfusions of blood product while was hospitalised for the surgical event.

Blood product transfusions

Five subjects (6.2%) in the efficacy population (4 [5.9%] in the PP population) required any blood product transfusion. All 5 subjects each underwent a major knee surgery. The median amount of transfused blood product for these 5 subjects was 910.0 mL and ranged from 250 to 1530 ml. Blood loss was assessed as less than expected for 4 of these subjects (3 with excellent haemostatic efficacy at discharge and 1 with good haemostatic efficacy) and as more than expected for the remaining subject (with excellent haemostatic efficacy at discharge).

Usage of the investigational medicinal product

Details on the usage of Voncento SP during the entire study are as follows: 29 subjects were included in the prophylaxis subgroup and 51 subjects in the prevention subgroup; 1 subject received Voncento as

on-demand therapy. Furthermore, 62 subjects took Voncento as treatment for a bleeding event, 18 prior to and during surgery, and 17 after surgery. The median average Voncento SP dose per infusion was 26.6 IU/kg body weight and ranged from 14 to 40 IU/kg.

Among the 64 subjects with at least 1 bleeding event during the study, 40 subjects (62.5%) (9 [50.0%] in the prophylaxis subgroup and 31 [68.9%] in the prevention subgroup) had bleeding events that each required either no or only 1 Voncento infusion. This includes 10 subjects who had a total of 12 bleeding events (5 subjects with 6 such events each in the prophylaxis and the prevention subgroups) that were reported as not being treated with Voncento. Four of these subjects received Voncento shortly (within <2 h) after the bleeding event, 3 subjects had received Voncento on the same day prior to the bleeding event, and for 2 subjects Voncento infusions given on the day of the bleeding event were related to a surgical event on that day. These latter 2 subjects, both from the prophylaxis subgroup, had only 1 bleeding event during the entire study. The Investigator assessed the haemostatic efficacy for all these 12 events, as excellent in 9 cases and as good in the remaining 3 cases.

Ancillary analyses

The efficacy data of the 3 adolescent subjects two treated for prophylaxis and 1 for prevention have been submitted by the applicant. None required surgery during the course of the study.

The 3 adolescent subjects in the study received 74, 62, and 54 infusions at an average dose per infusion of 40.2, 32.7 and 34.8 IU/kg, respectively, for bleeding or prophylaxis. These average doses were slightly higher than the mean doses per infusion reported for the efficacy population as a whole.

Summary of main studies

The following tables 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).

Table 20: 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	open-label, uncontrolled 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 (all subjects) 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 are enrolled in Arm 3.
Endpoints and definitions for Arm 2 only		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
		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	20 April 2011		

Results and Analysis Only the main results are summarized here

Analysis description	**Primary Analysis**
Analysis population	Efficacy population: all subjects who participated in the efficacy component of the study (either for set prophylaxis or have experienced at least 1 NSB event) and who received at least 1 dose of study product and who have at least 1 post-baseline haemostasis assessment by an investigator.
Primary Analysis	*Investigator's assessment of haemostatic efficacy per bleeding event* There was a haemostatic efficacy assessment in 405 of 538 events as follows: Excellent in 371/405 (91.6%); Good in 27/405 (6.7%); Moderate in 7/405 (1.7%) *Subject's assessment of haemostatic efficacy per day of bleeding event, all days* Excellent in 476/602 (79.1%); Good in 104/602 (17.3%); Moderate in 21/602 (3.5%) and None in 1/405 (0.2%) *Number of Bleeding Events During the Study: Total number and number per subject* A total of 538 NSB events were reported during the study. The majority of NSB events were spontaneous (534 events [99.3%]), minor (527 [98.0%]), mucosal (422 [78.4%]), and were treated at home (380 [70.6%]). *Blood Transfusion* 1 subject in the efficacy population required any blood product transfusion:

	Median number of bleeding events		19	
	Range		2 - 82	
	Median Number of infusions		19.5	
	Range		3 - 92	
	Median average dose per infusion (IU/kg)		39	
	Range		15 - 33	

Table 21: Summary of efficacy for Study CSLCT-BIO-07-47

Title: A Phase II, multicentre, double-blinded, randomised, cross-over study to evaluate efficacy, safety, and pharmacokinetics of Voncento in subjects with haemophilia A		
Study identifier	CSLCT-BIO-07-47	
Design	double-blind, randomised, cross-over Altogether, the study consisted of 4 periods: Screening period of up to 14 days. Part 1 was a multicentre, double-blind, randomised, cross-over study to evaluate the PK and safety of Voncento SP compared to Voncento RP. Part 2 of up to 6 months of Voncento SP as required, for a minimum of 50 exposure days (efficacy component, all subjects). Part 3 of up to 8 days (repeat PK assessment of the PK component, PK subjects only) consisted of a single dose of Voncento SP on Day 180 with PK samples collected on Days 180, 181, and 182.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	6 months or until 50 exposure days reached not applicable not applicable
Hypothesis	For the pharmacokinetic assessment, the PK and safety of Voncento SP was compared with that of Voncento RP. For the Clinical efficacy assessment, there is no comparator arm or statistical comparison with historical or bibliographic data	
Treatments groups	Prophylaxis Sub-group	Defined as: ≥90% of the Voncento infusions in Part 2 (excluding the first infusion) were applied ≤3 days after the previous Voncento infusion, excluding subjects of the on-demand subgroup.
	Prevention Sub-group	<90% of the Voncento infusions in Part 2 (excluding the first infusion) were applied ≤3 days after the previous Voncento infusion, excluding subjects of the on-demand subgroup.
	On-demand Sub-group	All Voncento infusions in Part 2 were given due to bleedings or surgeries, but none for prophylaxis or prevention.

Endpoints and definitions		Haemostatic Efficacy	- Assessment of haemostatic efficacy by the Investigator - Any blood product transfusion requirements, and the number of treatments/units required to resolve the event - FVIII concentrate usage: number of infusions, IU/kg per event, month and per year. - Assessment of blood loss during any surgical procedure - Factor VIII levels will be assessed to determine the minimum pharmacokinetic parameters
		The safety of Voncento in subjects with Haemophilia A	- the nature and incidence of adverse events - the development of FVIII inhibitors
Database lock	Interim : 26 March 2010 / final 27 August 2010		

Results and Analysis

Analysis description	**Primary Analysis**
Analysis population and time point description	Efficacy population
Primary Analysis	*Investigator's assessment of haemostatic efficacy per bleeding event* There was a haemostatic efficacy assessment in 656 of 667 events as follows: Excellent in 396/656 (60.4%); Good in 236/656 (36.0%); Moderate in 23/656(3.5%) None 1/656 (0.2%). The pattern of efficacy was similar in the prophylaxis and prevention subgroups *Subject's assessment of haemostatic efficacy per day of bleeding event, all days* Excellent in 509/944 (53.9%); Good in 321/944 (34.0%); Moderate in 104/944 (11.0%) and None in 10/944 (1.1%) *Blood Transfusions* 5 subjects in the efficacy population, each of whom underwent major knee surgery, required a blood transfusion. The median amount of transfused blood product for these 5 subjects was 910.0 mL and ranged from 250 to 1530 mL. Blood loss was assessed as less than expected for 4 of these subjects (3 with excellent haemostatic efficacy at discharge and 1 with good haemostatic efficacy) and as more than expected for the remaining subject (with excellent haemostatic efficacy at discharge;

Descriptive statistics and estimate variability	Treatment group	Prophylaxis	Prevention	Pre-and during surgery
	Number of subject	29	51	18
	Median number of bleeding events	1.0	9.0	n/a
	Range	0 - 18	0 - 44	
	Median number of bleeding events per month in Month 1	0.0	1.0	n/a
	Range	0 - 5	0 - 8	

	Median number of infusions Range	per bleeding event 10.0 1 - 50	 1.5 1 - 8
	Median of Average Dose per infusion Range	30.0 IU/kg 15 - 33	41.5 IU/kg 21 - 59
Notes	17 subjects in the prophylaxis and prevention subgroups did not experience a bleed		

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

N/A

Clinical studies in special populations

No clinical studies in special populations have been conducted (see discussion on clinical efficacy).

Supportive studies

- **Study CSLCT-BIO-03-97 (Von Willebrand Disease)**

Study CSLCT-BIO-03-97 was an open-label, multi-centre designed to evaluate the safety and efficacy of Voncento in patients with VWD. The study involved patients with a diagnosis of VWD who required prophylactic therapy, had a non-surgery bleed or were undergoing surgery. Initially, the study was designed to include adult subjects (aged ≥18 years) only, but following a protocol amendment children could also be recruited into the study, which led to the inclusion of one 3-year-old child.

The objectives of this study were to evaluate the efficacy and safety of Voncento RP in the treatment of NSB events, in the management of surgery procedures and prophylactic therapy in subjects with VWD where DDAVP treatment was deemed by the investigator to be ineffective, inadequate, or contraindicated. Subjects were to be treated for 12 months. The dose and frequency of human coagulation FVIII/VWF complex were determined by the investigator based on the subject's weight, their VWF:RCo levels and/or factor VIII coagulant activity (FVIII:C), and the requirement for treatment (prophylaxis, non-surgery bleeding, or surgery).

Results

The study was conducted from December 2004 until May 2007. A total of 23 subjects were recruited and grouped according to the first reason for requiring treatment (treatment event). The groups were: major surgery, minor surgery, NSB event, and prophylaxis. There were 17 initial surgical events: 9 major and 8 minor. Two subjects were enrolled into the study with an NSB event as their initial event and 4 subjects required prophylactic treatment. Seventeen subjects completed the 12-month study duration. Four subjects were withdrawn as a result of the study termination by the Sponsor, 1 subject was lost to follow up, and 1 subject was transferred to a non-trial site for treatment.

Twelve subjects were male and 11 were female; all were Caucasian with the exception of 1 Asian and 1 subject whose race was reported as "other". The mean age was 47.2 years (range: 3-85 years) and the mean weight was 75.0 kg (range: 17.2-110.0 kg). The 3-year-old child was the only subject aged <18 years. Seven subjects presented with Type 1 VWD, 2 with Type 2A VWD, 6 with Type 2M VWD, 7 with Type 3 VWD, and 1 subject with Type 2 VWD where the subtype was unknown.

Subjects received a mean daily dose per treatment event (NSB event or surgical procedure) of 34.1 IU FVIII/kg, for a median duration of 2 days (range: 1-24) per event (7.5 days [range: 3- 24 days] for major surgery; 2.0 days [range: 1-8 days] for minor surgery; 2 days [range: 1- 10 days] for NSB events.

The median number of infusions per treatment event was higher for major surgery (10 infusions; range: 3-35) than for minor surgery (2 infusions; range: 1-14) or for non-surgery bleedings (2 infusions; range: 1-12). The median overall exposure to human coagulation FVIII/VWF complex was 8 days (range: 1-197 days). In the prophylactic group, the overall median number of infusions was 62 (range: 55-199) and the median exposure was 62 days (range: 53-197 days).

Haemostatic assessment

Ten major surgical events, 19 minor surgical events, and 31 NSB events (including 22 spontaneous NSB events in the 4 subjects on prophylaxis) were reported during the study.

In the ITT Set, haemostatic efficacy for all minor and major surgery events, and patients on prophylactic therapy was rated by the investigator as Good or Excellent at all-time points. For the non-surgery bleed events with investigator assessments four events were rated as Good or Excellent at all-time points, one event was rated as Moderate, and one event was rated as None (severe and uncontrolled bleeding) for the first 3 days before haemostasis was reached on Day 4 when the event was rated as Good and remained that way thereafter. Similar results for haemostatic efficacy were obtained in the PP Set.

FVIII:C/VWF

Plasma levels of FVIII:C were low (< 50%) for the majority of surgery events in the ITT Set (minor surgery: 10 [76.9%] of 13 events; major surgery: 7 [77.8%] of 9 events) before administration of Voncento (Table 22). On Day 1 the levels increased to within the normal range for most events (minor surgery: 90.0% of events; major surgery: 100.0% of events) and levels remained in the normal range for the majority of events up to and including the Post-treatment Visit. At the 30-Day Follow-up Visit, plasma levels had fallen back to low once more in the majority of surgery events. Two patients had high FVIII:C levels (> 200%) during treatment for their major surgery events. The plasma levels of VWF:RCo were low (< 45%) for most surgery treatment events (minor surgery: 11 [84.6%] of 13 events, major surgery: 9 [100.0%] of 9 events) prior to the first dose of Voncento. On Day 1, the levels had increased to within the normal range in 50.0% of minor surgery events and 88.9% in major surgery events, and levels remained in the normal range for the majority of events up to Day 5. Subsequent to Day 5, the levels ranged between low and normal (< 200%). The levels for the majority of events at the Post-treatment Visit were < 45% (minor surgery: 7 [53.8%] of 13 events; major surgery: 4 [57.1%] of 7 events). The plasma levels for VWF:Ag and VWF:CB followed a similar pattern to FVIII:C levels for both minor and major surgery events. In the non-surgery bleed events, plasma levels of FVIII:C and VWF:RCo stayed low or within the normal range at all time points; VWF:Ag and VWF:CB levels were similar. Data were often unavailable which may have been due to patients self-administering Voncento at home without contacting the study site and/or the failure of the study site personnel to collect the required laboratory samples. This has resulted in the numbers in this treatment group being too small to show any definitive movement up or down in plasma levels. The efficacy results for the PP Set were similar to those of the ITT Set (data not shown).

Table 22: Summary of Plasma Levels of FVIII:C and VWF for the First 4 Days and Post-treatment Visit, Major Surgery Treatment Group, Intent-to-Treat Set

	Major Surgery Treatment Group (N=10)			
	FVIII:C	VWF:RCo	VWF:CB	VWF:Ag
Day 0	n=9	n=9	n=9	n=9
Mean (SD)	25.6 (19.6)	10.1 (10.7)	16.4 (15.1)	19.7 (17.9)
Median; Min, Max	20.0; 3, 58	5.0; 0, 30	11.0; 0, 43	17.0; 0, 50
Low[a]	7 (77.8%)	9 (100.0%)	9 (100.0%)	7 (77.8%)
Normal	2 (22.2%)	0	0	2 (22.2%)
High	0	0	0	0
Day 1	n=9	n=9	n=9	n=9
Mean (SD)	89.6 (29.6)	81.2 (41.1)	95.4 (50.4)	167.2 (87.7)
Median; Min, Max	90.0; 53, 147	80.0; 28, 171	95.0; 28, 190	153.0; 66, 323
Low[a]	0	1 (11.1%)	2 (22.2%)	0
Normal	9 (100.0%)	8 (88.9%)	7 (77.8%)	6 (66.7%)
High	0	0	0	3 (33.3%)
Day 2	n=9	n=9	n=9	n=9
Mean (SD)	107.4 (40.6)	94.3 (61.8)	92.3 (39.9)	179.2 (96.2)
Median; Min, Max	93.0; 67, 200	89.0; 13, 228	90.0; 33, 151	156.0; 83, 401
Low[a]	0	1 (11.1%)	1 (11.1%)	0
Normal	9 (100.0%)	7 (77.8%)	8 (88.9%)	6 (66.7%)
High	0	1 (11.1%)	0	3 (33.3%)
Day 3	n=6	n=6	n=6	n=6
Mean (SD)	112.5 (56.4)	92.5 (57.6)	87.2 (67.0)	168.8 (100.3)
Median; Min, Max	99.0; 61, 213	74.0; 34, 186	74.0; 27, 215	136.0; 75, 343
Low[a]	0	1 (16.7%)	2 (33.3%)	0
Normal	5 (83.3%)	5 (83.3%)	4 (66.7%)	4 (66.7%)
High	1 (16.7%)	0	0	2 (33.3%)
Post-treatment	n=8	n=7	n=7	n=7
Mean (SD)	101.8 (61.8)	42.6 (24.5)	52.1 (22.9)	118.1 (54.6)
Median; Min, Max	89.0; 40, 237	35.0; 16, 90	58.0; 19, 76	115.0; 62, 205
Low[a]	1 (12.5%)	4 (57.1%)	2 (28.6%)	0
Normal	6 (75.0%)	3 (42.9%)	5 (71.4%)	6 (85.7%)
High	1 (12.5%)	0	0	1 (14.3%)

Abbreviations: FVIII:C = factor VIII:coagulant activity; N = number of treatment events in the Intent-to-Treat Set within the relevant treatment group; n = number of treatment events with a corresponding result; VWF:Ag = von Willebrand factor:antigen; VWF:CB = von Willebrand factor:collagen binding capacity; VWF:RCo = von Willebrand factor:ristocetin co-factor activity.

[a] FVIII:C = Low < 50%; Normal 50%-200%; High > 200%. VWF:RCo = Low < 45%; Normal 45%-200%; High > 200%. VWF:CB = Low < 50%; Normal 50%-400%; High > 400%. VWF:Ag = Low < 40%; Normal 40%-200%; High > 200%.

Blood Loss and Transfusions

In the ITT Set, over 80% of the surgery events that were assessed for blood loss were considered to have had less or equivalent blood loss for minor or major surgery than would normally be expected in an event involving a patient without a bleeding disorder. Four patients received blood transfusions during the study for their bleeding and surgery events.

Voncento Administration

For the major surgery treatment group, a longer treatment period and more infusions with Voncento were required compared with the minor surgery and non-surgery bleed groups. The mean total dose of FVIII:C in Voncento required to resolve an event was highest for patients in the major surgery group compared with patients in the non-surgery bleed group and minor surgery group. Mean daily dose per treatment event was slightly higher for patients in the major surgery group compared with patients in the minor

surgery group (41.35 IU/kg/day compared with 33.48 IU/kg/day) and was clearly higher compared with the non-surgery bleed group (27.36 IU/kg/day).

- **Study CSLCT-BIO-95-41 (Haemophilia A)**

Study CSLCT-BIO-95-41 was an open, multicentre study to assess the safety, tolerability and efficacy of Voncento in patients with severe haemophilia A. This study was carried out in 1998 – 1999 in Australia and New Zealand.

The objectives of the study were: assessment of the safety and tolerability (via the collection of adverse event data) of Voncento, assessment of the efficacy of Voncento in a study population with severe haemophilia A and assessment of the potential for development of "silent inhibitors" (inhibitors not detectable by Bethesda Unit Assay) by repeating pharmacokinetic assessments of Voncento in a minimum of 10 subjects who participated in the pharmacokinetic study of Voncento. A 20% change in a pharmacokinetic parameter (half-life or AUC) will be considered of clinical significance.

Results

A total of 30 subjects were enrolled into the study, including all 16 subjects from the preceding PK study CSLCT-BIO-95-30. Four subjects were withdrawn from the study: 1 subject each due to AEs (recurrent episodes of chest pain, back pain, and anxiety 3 to 5 minutes post-infusion), a protocol violation (the subject received AHF [HP]), a scheduled elective surgery, and a suspected therapeutic failure.

All subjects were male. The mean age was 35.3 years (range: 16-62 years) and the mean body weight was 76.4 kg (range: 50-102 kg). Two adolescent subjects (aged 16 and 17 years) were included. Twenty-five subjects (83.3%) were of Caucasian race, 2 were Asian, and 1 was Fijian Indian. Race was not reported for 2 subjects.

The screening for FVIII inhibitors revealed no subjects with inhibitor at study entry and no subjects developed a FVIII inhibitor at any point in the study.

Subjects received human coagulation FVIII/VWF complex as replacement therapy for a period of 6 months. All 30 subjects received at least 1 infusion. A total of 1019 infusions were administered to 30 subjects over the study period of 12 months, resulting in 980 exposure days. Nine subjects achieved ≥50 exposure days, Overall, 390 infusions (38.3%) were administered for spontaneous bleeding events, 273 (26.8%) as prophylaxis, and 248 (24.3%) for trauma episodes. The reason for use was reported as “other” for 99 infusions and was missing for 9 infusions. The total number of administrations of human coagulation FVIII/VWF complex per subject ranged from 6 to 85.

The average number of vials used per infusion ranged from 3.1 to 10.7. The average volume infused ranged from 15.3 to 53.4 mL and the average total dose of human coagulation FVIII/VWF complex ranged from 757.5 to 2,671.4 IU. The overall average dose per infusion was 1,390 IU. The total dose of human coagulation FVIII/VWF complex per subject ranged 66.7 to 1,895.2 IU/kg and the total number of exposure days per subject ranged from 6 to 84 days with a mean of 32.6 days. A small number of subjects required more than 1 infusion per day to treat major bleeding events.

The haemostatic efficacy of the IMP was assessed as excellent for 124 (15.9%) of the 782 administrations graded by subjects for efficacy, as good for 491 administrations (62.8%), as moderate for 136 administrations (17.4%), and as poor for 31 administrations (4.0%). For 237 administrations of human coagulation FVIII/VWF complex, no haemostatic efficacy assessment was reported (including 137 prophylactic infusions, some initial infusions, and PK infusions). Twenty-one of the 31 “poor” treatment responses were reported following treatment for a spontaneous bleeding event, 1 for trauma, 3 for prophylaxis and 6 for other reasons (in 3 subjects undergoing other treatments). The most frequently reported response was excellent for 4 subjects (13.3%), good for 18 subjects (60.0%), and moderate for

the remaining 8 subjects (26.7%). The 2 adolescent subjects evaluated the haemostatic efficacy of human coagulation FVIII/VWF complex as either good or excellent, where the haemostatic efficacy assessment was available.

The investigator or study nurse classified the subjects' response for the first infusion, and subjects evaluated the haemostatic efficacy during home therapy thereafter using a 4-point scale with the outcomes excellent, good, moderate, or poor. However, not all infusions were categorised according to the subjects' response to therapy (e.g. infusions administered for prophylaxis were not always perceived by subjects as evaluable). The haemostatic efficacy of the IMP was assessed as excellent for 124 (15.9%) of the 782 administrations graded by subjects for efficacy, as good for 491 administrations (62.8%), as moderate for 136 administrations (17.4%), and as poor for 31 administrations (4.0%). For 237 administrations of human coagulation FVIII/VWF complex, no haemostatic efficacy assessment was reported (including 137 prophylactic infusions, some initial infusions, and PK infusions). Twenty-one of the 31 "poor" treatment responses were reported following treatment for a spontaneous bleeding event, 1 for trauma, 3 for prophylaxis and 6 for other reasons (in 3 subjects undergoing other treatments). The most frequently reported response was excellent for 4 subjects (13.3%), good for 18 subjects (60.0%), and moderate for the remaining 8 subjects (26.7%). The 2 adolescent subjects evaluated the haemostatic efficacy of human coagulation FVIII/VWF complex as either good or excellent, where the haemostatic efficacy assessment was available.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The design and conduct of the pivotal trial CSLCT-BIO-07-47 was in accordance with CHMP guidelines. A number of findings were identified with regard to the conduct of the pivotal study CSLCT-BIO-08-54 by the EMA GCP inspection and the independent audit initiated by the Applicant but overall the integrity of the efficacy and safety data for both studies was found not to be compromised (see section 2.4.1.) as the findings identified did not have an impact on centrally important trial parameters such as diagnosis or efficacy and safety evaluations.

Efficacy data and additional analyses

- *Haemophilia A*

In the pivotal study, in the entire efficacy population, a total of 667 bleeding events were reported during the study, corresponding to a mean number of bleeding events per subject of 8.2. Haemostatic efficacy was assessed by the Investigator as either excellent or good for the vast majority of subjects for bleeding events or surgical events. The subjects assessed the haemostatic efficacy of Voncento as excellent on 53.9% , as good on 34.0%, as moderate on 11.0%, and as poor on 1.1% of bleeding days.

Five subjects (6.2%) in the efficacy population required blood product transfusion. For more than 97% of the 37 surgical events blood loss was assessed as less than (40.5%) or equivalent to (56.8%) the blood loss expected for a subject without a bleeding disorder.

According to definitions based on the number of days between Voncento infusions, 29 subjects were included in the prophylaxis subgroup and 51 subjects in the prevention subgroup; 1 subject received Voncento as on-demand therapy. The mean number of bleeding events per subject was considerably lower in the prophylaxis subgroup (3.5 bleeding events) than in the prevention subgroup (10.7 bleeding events). Among the subjects with at least 1 bleeding event during the study, 9 subjects (50.0%) in the prophylaxis subgroup and 31 (68.9%) in the prevention subgroup required no or only 1 Voncento infusion

per bleeding event. Haemostatic efficacy results within these subgroups were similar to those in the overall efficacy population.

The median average Voncento SP dose per infusion was 26.6 IU/kg body weight and ranged from 14 to 40 IU/kg, with 62 subjects taking Voncento as treatment for a bleeding event, 18 prior to and during surgery, and 17 after surgery. Overall, 13.9% of bleeding events required more than 1 Voncento infusion.

Results in the per protocol (PP) population were similar to those seen in the efficacy population. Furthermore, efficacy results, including the usage of Voncento SP, in the 3 adolescent subjects were not different from the efficacy results in the efficacy population.

- *Von Willebrand's Disease*

In the pivotal Study CSLCT-BIO-08-54, efficacy in the on-demand treatment of non-surgical bleeds, studied in 20 subjects for 12 months, was reported by the investigator as being excellent in 371/405 (91.6%) of the bleeds, good in 27/405 (6.7%) and moderate in 7/405 (1,7%). These bleeds included 7 major mucosal bleeds as required by the relevant CHMP guideline. The subject's assessment of hemostatic efficacy per day of bleeding event on all bleeding days was excellent in 476/602 (79.1%), good in 104/602 (17.3%), moderate in 21/602 (3.5%) and none in 1/602 (0.2%).

A total of 538 NSB events were reported during the study, resulting in a median number of NSB events per subject of 19 (range: 2-82). Seven subjects had a total of 132 NSB events that did not require treatment with Voncento and which were therefore considered not evaluable.

Additional data on 10 major surgical events was provided for VWD subjects from the supportive study CSLCT-BIO-03-97 and this demonstrated that in 88% of subjects blood loss was less than or equivalent to that expected in a patients with no bleeding diathesis. Voncento was used in 10 major and in 15 minor surgeries. In those surgeries, where hemostatic efficacy was reported, efficacy was rated on day 1 as excellent in 10/11 of the minor surgeries and in 8/10 of the major surgeries, and as good in the other 2 major surgeries and 1 minor surgery.

Two investigator-led efficacy studies, one reported by Shortt et al (2007) and another by Howman et al (2010), provide supportive evidence of efficacy in VWD (data not shown).

Assessment of paediatric data on clinical efficacy

There are only very limited paediatric data from the pivotal trials:

Study CSLCT-BIO-08-54 included 3 adolescent subjects.

Study CSLCT-BIO-07-47 included 3 adolescent subjects for prophylaxis / prevention.

According to the relevant CHMP guideline on VWF products, paediatric data could be submitted post-authorisation. The recently adopted CHMP guideline on FVIII products requires pediatric data to be available pre-authorisation. However, a PIP has been submitted and the PDCO has agreed that the efficacy /safety trials for both indications in children < 12 years should be initiated pre-authorisation and clinical study results be submitted post-authorisation.

These are study CSLCT–BIO-08-53 in previously treated children from birth to less than 12 years of age with hemophilia A and study CSLCT–BIO-08-52 in subjects aged birth to < 12 years old with VWD.

The applicant also intends to submit study CSLCT–BIO-10-67 in children from 1 month to less than 12 years of age with hemophilia A who have developed high responding antibodies to FVIII post-authorisation.

Additional expert consultation

As requested by CHMP, the BPWP was consulted on the following points:

1) Post-marketing data in paediatric VWD patients < 12 years of age

BPWP members noted that the "Guideline on the clinical investigation of human plasma derived von Willebrand factor products" (CPMP/BPWG/220/02) and the core SmPC for VWF products ((CPMP/BPWG/278/02) were adopted in 2005 before the paediatric regulation was implemented.

With the response to the D180 LoI, the applicant submitted a study protocol for an efficacy and safety PMS in 20 VWD patients > 12 years (CSLCT-BIO-12-83), however, enrolment is not open to children <12 years. Data in at least 8 paediatric VWD patients < 12 years are collected in an on-going clinical study (CSLCTBIO-08-52). The final study report, including PK data, is expected in 2014. BPWP members noted the Rapporteurs' conclusion that the clinical data is sufficient to support approval of the VWD indication in patients > 12 years, as applied for by the applicant, and taking into account that efficacy and safety data in a further 20 patients > 12 years will be investigated post-authorisation. BPWP advised that if CHMP considers that there is currently insufficient data to recommend use in children under 12 years, this should be addressed in the SmPC according to the approach in the core SmPC for FVIII products since this in line with the latest SmPC guideline. Therefore, the age range > 12 years would be indicated in section 4.1 of the SmPC. In section 4.2 of the SmPC a statement informing about limited data in children would be included.

A two-step approach is recommended for the requirements for paediatric data in VWD patients. The first-step is the submission and evaluation of the final clinical study report (CSLCT-BIO-08-52) investigating 8 paediatric patients < 12 years in 2014. Once these data are available and provided the evaluation is positive, the post-marketing study >12 years (CSLCT-BIO-12-83) should be opened to allow enrolment of patients < 12 years. The company's agreement to this strategy should be reflected in the Risk Management Plan.

2) Post-marketing data in paediatric haemophilia A patients < 12 years of age

While the guideline on FVIII products (EMA/CHMP/BPWP/144533/2009) gives clear guidance on the number of patients to be enrolled in the PMS for recombinant FVIII products, it states that for plasma-derived products a smaller number of patients can be enrolled on a case-by-case basis and if adequately justified by the applicant.

The applicant proposes to include 100 haemophilia A patients > 12 years in the PMS for Voncento, which is considered acceptable by the Rapporteurs taking account the currently available clinical data, but does not propose to enrol children < 12 years. In the on-going paediatric study (CSLCT-BIO-08-53), at least 20 patients < 12 years will be studied. A further 10 children < 12 years will be studied in study CSLCT–BIO-10-67.

BPWP members noted the Rapporteurs' conclusion that the clinical data is sufficient to support approval of the haemophilia A indication in patients > 12 years as applied for by the applicant. BPWP advised that if CHMP considers that there is currently insufficient data to recommend use in children under 12 years, the indication would be restricted in section 4.1 of the SmPC and in section 4.2 a statement on limited data in children < 12 years would be included, in accordance with the core SmPC for FVIII products. BPWP members acknowledge the difficulties in enrolment of paediatric patients in clinical studies with plasma-derived FVIII products in Europe, nevertheless, the data from the on-going paediatric study should be supplemented with paediatric data collected in the post-authorisation phase, following the same step-wise approach as described above for VWD. Therefore, once the data are available from paediatric study (CSLCT-BIO-08-53) and provided the evaluation is positive, the post-marketing study

>12 years (CSLCT-BIO-12-78) should be opened to allow enrolment of patients < 12 years. The company's agreement to this strategy should be reflected in the Risk Management Plan.

2.5.4. Conclusions on the clinical efficacy

Adequate efficacy has been provided for Haemophilia A (prophylaxis and treatment) and for Von Willebrand Disease (treatment) in patients over the age of 12 years. The data provided were robust and in compliance with CHMP guidelines.

The CHMP taking into account that Voncento is in principle a conventional plasma-derived product with documented efficacy/safety and post marketing experience, decided that there is no basis for an age restriction in the indications. In line with the core SmPC for factor VIII products (EMA/CHMP/BPWP/1691/1999, rev. 1) it will be reflected in section 4.2. of the SmPC that the safety and efficacy of Voncento in children < 12 years have not been established and no data are available.

As recommended in the relevant CHMP guidelines for clinical investigation of factor VIII and Von Willebrand factor products (EMA/CHMP/BPWP/144533/2009 and CPMP/BPWG/220/02) post authorisation studies aiming to assess the long–term efficacy of Voncento in both indications are included in the RMP (see also discussion on clinical safety and RMP sections).

2.6. Clinical safety

A tabular listing of studies providing safety data is provided in Table 23 for haemophilia A and in Table 24 for VWD.

Table 23: Tabular listing of studies providing safety data for haemophilia A

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 variables
Pivotal safety and efficacy study in haemophilia A							
CSLCT-BIO-07-47	II March 2009 - October 2010	15 Bulgaria, Republic of Macedonia, Poland, and Russia	Double-blind, randomised, cross-over (initial PK); open-label, uncontrolled (efficacy component, repeat PK)	To assess the efficacy of human coagulation FVIII/VWF complex and to assess the comparability of the PK of Biostate RP and Biostate SP (human coagulation FVIII/VWF complex) in subjects with severe haemophilia A.	Initial PK: Biostate RP, Biostate SP (cross-over), single dose of 50 IU/kg. Efficacy component: Biostate SP (human coagulation FVIII/VWF complex); prophylaxis or on-demand; dose as required. Repeat PK: Biostate SP (human coagulation FVIII/VWF complex), single dose of 50 IU/kg.	81 (includes 17 PK subjects; 15 repeat) Males 33.1 ± 12.8 years (13-68 years), including 3 adolescents aged 13-15 years PK component: 36.5 ± 12.7 years (18-57 years)	Evaluation of AEs, biochemistry, haematology, FVIII inhibitors, physical examination, and vital signs.
Supportive safety and efficacy studies in haemophilia A							
CSLCT-BIO-95-30	II March -June 1998	4 Australia	Open-label, multi-centre	To assess the PK of Biostate in a study population with severe haemophilia A, and to collect safety data on Biostate	Biostate RP Single dose of 50 IU/kg.	16 Males 36.4 ± 11.71 years (17-53 years), including 1 adolescent aged 17 years	Evaluation of AEs, biochemistry, haematology, urinalysis, and vital signs.

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 variables
CSLCT-BIO-95-41	II/III March 1998 - March 1999	6 Australia and New Zealand	Open-label, uncontrolled, multi-centre	To assess the safety, tolerability, and efficacy of Biostate in a study population with severe haemophilia A, and to assess the potential for development of "silent inhibitors" by repeating PK assessments of Biostate in a subjects who participated in the PK study of Biostate (CSLCT-BIO-95-30).	Biostate RP Dosing as required for prophylaxis or for bleeding event. Repeat PK: single dose of 50 IU/kg, 3-6 months after screening.	30 (includes 16 PK subjects; 8 repeat) Males 35.3 ± 11.8 years (16-62 years), including 2 adolescents aged 16 and 17 years	Evaluation of AEs, biochemistry, haematology, urinalysis, virology, FVIII inhibitors, physical examination, and vital signs.

AE = adverse event; FVIII = factor VIII; haem A = haemophilia A; IU = International Unit; PK = pharmacokinetic(s); RP = reference product; SD = standard deviation; SP = study product; VWF = Von Willebrand factor.

Table 24: Tabular listing of studies providing safety data for Von Willebrand Factor

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 study in VWD							
CSLCT-BIO-08-54	II/III June 2009 - March 2011 (completion of first 12 months)	6 Brazil, Bulgaria, Poland, Russia, and Ukraine	Open-label multi-centre study	To investigate the initial and repeat PK profile of human coagulation FVIII/VWF complex in subjects with severe VWD. To assess the haemostatic efficacy of human coagulation FVIII/VWF complex 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 human coagulation FVIII/VWF complex 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.
Supportive safety and efficacy studies in VWD							
CSLCT-BIO-00-75	I January -May 2003	5 Australia	Single-blind, randomised, cross-over, multi-centre	To evaluate the PK of Biostate and AHF (HP) in subjects with VWD, in order to determine comparability	Biostate RP Single infusion of 60 IU VWF:RCo/kg (corresponding to 30 IU FVIII/kg).	12 (Type 1: 4, Type 2B: 2, Type 2M: 1, Type 3: 5) 8 males, 4 females 38 ± 11.9 years (19-58 years)	Evaluation of AEs, biochemistry, haematology, and vital signs.

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
CSLCT-BIO-03-97	II/III December 2004 - May 2007	8 Australia New Zealand	Open-label, multi-centre	To evaluate the efficacy and safety of human coagulation FVIII/VWF complex 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	N/A April 2003 - September 2005	3 Australia	Retro-spective	To evaluate the safety and efficacy of human coagulation FVIII/VWF complex 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.
Howman study	N/A April 2003 - February 2008	8 Australia New Zealand	Retro-spective	To evaluate the efficacy, safety, and dosing of human coagulation FVIII/VWF complex in the treatment and prevention of bleeding in children and adolescents with VWD.	Biostate 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) [b]	The nature and frequency of AEs and clinically significant changes in vital signs.

AE = adverse event; AHF (HP) = anti-haemophilic factor (high purity); DDAVP = 1-deamino-8-D-arginine vasopressin, desmopressin acetate; FVIII = factor VIII; FVIII:C = factor VIII coagulant activity; IMP = investigational medicinal product; IU = International Unit; N/A = not applicable; NSB = non-surgical bleeding; PK = pharmacokinetic(s); RP = reference product; SP = study product; VWD = Von Willebrand disease; VWF = Von Willebrand factor; VWF:RCo = Von Willebrand factor: Ristocetin Cofactor activity.

[a] Median.

[b] No differentiation was made between adolescents and children.

In all prospective clinical studies, safety was assessed through reporting of AEs, including serious AEs (SAEs) and AEs considered related to the study drug (adverse drug reactions [ADRs]), and the assessment of biochemistry, haematology, and vital signs. In addition, physical examinations were performed in pivotal studies CSLCT-BIO-07-47 and CSLCT-BIO-08-54, and in supportive study CSLCT-BIO-95-41. FVIII inhibitors were assessed in haemophilia A studies CSLCT-BIO-07-47 and CSLCT-BIO-95-41, and FVIII and VWF inhibitors were assessed in VWD study CSLCT-BIO-08-54. In supportive haemophilia A studies CSLCT-BIO-95-30 and CSLCT-BIO-95-41, urinalysis was also part of the safety assessments, as was a virology assessment in study CSLCT-BIO-95-41.

Patient exposure

A total of 168 subjects were exposed to human coagulation FVIII/VWF complex in the prospective clinical studies, including 111 subjects with haemophilia A and 57 subjects with VWD. Among the exposed subjects, 5 subjects with haemophilia A and 3 subjects with VWD were adolescents, ie, aged 12 - <18 years, and 1 subject with VWD was a 3-year-old child. An additional 43 adult subjects with VWD were exposed with human coagulation FVIII/VWF complex in the investigator-led Shortt study and 43 children and adolescents were exposed in the investigator-led Howman study.

Doses calculated for the treatment of haemophilia A were based solely upon the FVIII required to replace endogenous FVIII, while doses calculated for the treatment of VWD were based on VWF:RCo. In general doses were approximately 10 to 40 IU FVIII / kg in the hemophilia A studies CSL-CT-BIO-07-47 and CSL-CT-BIO-95-41 and 15 to 50 IU VWF:RiCo / kg in VWD study CSLCT-BIO-08-54. In study CSLCT-BIO-03-97 the mean daily dose per treatment event was 34 IU FVIII / kg.

Doses in the retrospective investigator-led Shortt and Howman studies were based on FVIII.

Adverse events

A total of 417 treatment-emergent adverse events (TEAEs, i.e. 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 CSLCTBIO-95-41, respectively) and 207 in VWD studies (72 in pivotal study CSLCT-BIO-08-54, 24 and 111 in supportive studies CSLCT-BIO-00-75 and CSLCT-BIO-03-97, respectively).

Two of the 8 adolescent subjects included in the prospective clinical studies experienced a total of 8 TEAEs, 1 additional adolescent in the Howman study had 1 AE, and the 3-year-old child in VWD study CSLCT-BIO-03-97 had a total of 6 TEAEs; In the Shortt study no adverse reactions to treatment were reported. Two bleeding events were reported but neither of these was considered to be associated with “lack of efficacy” or raised any safety concerns. In the Howman study there was 1 reported case of nausea in one adolescent, which was considered possibly related to human coagulation FVIII/VWF complex by the investigator.

An overview of the number of subjects experiencing at least 1 TEAE during the prospective clinical studies is provided by AE is summarized in table 25 below.

Table 25: Overview of treatment-emergent AEs in prospective clinical trials

	CSLCT-BIO-07-47	CSLCT-BIO-95-30	CSLCT-BIO-95-41	CSLCT-BIO-08-54	CSLCT-BIO-00-75	CSLCT-BIO-03-97
Any TEAEs	39 (48.1%)/143	1 (6.3%)/2	21 (70.0%)/65	14 (63.6%)/72	10 (83.3%)/24	22 (95.7%)/111
Possible related TEAEs	8 (9.9%)/18	1 (6.3%)/2	6 (20.0%)/23	2 (9.1%)/2	2 (16.7%)/5	2 (8.7%)/2
SAEs	4 (4.9%)/6	0	1 (3.3%)/1	1 (4.5%)/1	1 (8.3%)/1	2 (8.7%)/2
Possible related SAEs	0	0	0	0	0	0
AEs leading to permanent treatment discontinuation	1 (1.2%)/2	0	1 (3.3%)/1	0	0	0
Possibly related TEAEs leading to permanent treatment discontinuation	0	0	1 (3.3%)/1	0	0	0
death	0	0	0	0	0	0

Number (%) of subjects/number of TEAEs

In subjects with haemophilia A, the most commonly reported AEs were headache (11 subjects), viral infection (8 subjects; however, no cases of suspected transmission of hepatitis virus or parvovirus B19 occurred), arthralgia (8 subjects), and influenza (7 subjects). Similar to the studies in haemophilia A, in subjects with VWD headache was most commonly reported across all VWD studies (reported in 15 subjects). Other frequently reported AEs in the VWD studies were procedural pain (ie, post-operative pain) and nausea, reported in 7 subjects each. Frequencies of subjects with TEAEs reported during the prospective clinical studies for the most frequently reported TEAEs (>5% of subjects in any study) are summarized in table 26 below.

Table 26: Number of subjects with ≥ 1 TEAEs in clinical studies (events reported >5% in any of study)

	CSLCT-BIO-07-47	CSLCT-BIO-95-30	CSLCT-BIO-95-41	CSLCT-BIO-08-54	CSLCT-BIO-00-75	CSLCT-BIO-03-97
Any AEs	39 (48.1%)	1 (6.3%)	21 (70.0%)	14 (63.6%)	10 (83.3%)	22 (95.7)
Gastrointestinal disorders						
Abdominal pain	0	0	0	1 (4.5%)	0	2 (8.7%)
Constipation	1 (1.2%)	0	0	0	0	3 (13.0%)
Nausea	0	0	1 (3.3%)	0	1 (8.3%)	6 (26.1%)
Oral pain	0	0	0	0	0	3 (13.0%)
Toothache	3 (3.7%)	0	1 (3.3%)	2 (9.1%)	0	1 (4.3%)
Vomiting	1 (1.2%)	0	0	0	1 (8.3%)	3 (13.0%)
General disorders and administration site conditions		0				
Fatigue	0	0	2 (6.7%)	0	0	1 (4.3%)
Pain	1 (1.2%)	0	0	0	0	2 (8.7%)
Pyrexia	1 (1.2%)	0	1 (3.3%)	0	1 (8.3%)	2 (8.7%)
Infections and infestations		0				
infection	0	0	0	0	0	2 (8.7%)
Influenza	4 (4.9%)	0	3 (10.0%)	0	0	0
Nasopharyngitis	1 (1.2%)	0	0	2 (9.1%)	0	0

Pharyngitis	1 (1.2%)	00	1 (3.3%)	0	1 (8.3%)	0
Tonsillitis	1 (1.2%)	0	2 (6.7%)	0	0	0
Tooth abscess	0	0	0	0	1 (8.3%)	0
Upper resp tract infection	0	0	2 (6.7%)	0	1 (8.3%)	1 (4.3%)
Urinary tract infection	0	0	1 (3.3%)	0	0	2 (8.7%)
Viral infection	8 (9.9%)	0	0	0	1 (8.3%)	0
Injury, poisoning and procedural complications		0				
Procedural pain	1 (1.2%)	0	0	0	0	7 (30.4%)
Musculoskeletal pain		0				
Neck pain	0	0	0	0	1 (8.3%)0	0
Musckuloskeletal pain	1 (1.2%)		1 (3.3%)	0	0	1 (4.3%)
Arthralgia	7 (8.6%)		1 (3.3%)	0	0	0
Back pain	1 (1.2%)		2 (6.7%)	1 (4.5%)	0	2 (8.7%)
haemarthrosis	0		0	0	1 (8.3%)	0
Nervous system disorders						
Headache	5 (6.2%)	0	6 (20.0%)	4 (18.2%)	5 (41.7%)	6 (26.1%)
Dizziness	0	0	1 (3.3%)	0	1 (8.3%)	0
Dyseusia	1 (1.2%)	0	0	0	1 (8.3%)	0
Psychiatric disorders						
insomnia	0	0	0	0	0	2 (8.7%)
Reproductive system and breast disorders						
Ovarium cyst rupture	0	0	0	0	1 (8.3%)	0
Respiratory, thoracic and mediastinal disorders						
cough	0	0	0	1 (4.5%)	0	2 (8.7%)
rhinitis	0	0	1 (3.3%)	0	1 (8.3%)	0
Skin and subcutaneous tissue disorders						
Hyperhidrosis	0	0	1 (3.3%)	0	1 (8.3%)	0
Vascular disorders						
Hypertension	3 (3.7%)	0	1 (3.3%)	1 (4.5%)	0	3 (13.0%)
Hypertensive crisis	0	0	0	2 (9.1%)	0	0

Number (%) of subjects/number of TEAEs

The incidence of AEs assessed as possibly, probably or definitely related to study medication in clinical studies is presented in table 27.

Table 27: Incidence of AEs assessed as possibly, probably or definitely related to study medication in clinical studies

	CSLCT-BIO-07-47 Haem A	CSLCT-BIO-95-30 Haem A	CSLCT-BIO-95-41 Haem A	CSLCT-BIO-08-54 VWD	CSLCT-BIO-00-75 VWD	CSLCT-BIO-03-97 VWD
Total	18 (100)	2 (100)	23 (100)	2 (100)	5 (100)	2 (100)
Cardiac disorders						
Tachycardia	4 (22.2%)	0	0	0	0	0
Eye disorders						
Eye oedema	0	0	0	1 (50.%)	0	0
Gastrointestinal disorders						
Constipation	2 (11.1%)	0	0	0	0	0
Nausea	0	0	0	0	1 (20.0%)	0
Paraesthesia oral	2 (11.1%)	0	0	0	0	0
Vomiting	0	0	0	0	1 (20.0%)	0
General disorders and administration site conditions						
Asthenia	1 (5.6%)	0	0	0	0	0
Chest pain	0	0	1 (4.3%)	0	0	0
Chest discomfort	0	0	1 (4.3%)	0	0	0
Fatigue	0	0	1 (4.3%)	0	0	0
Feeling hot	3 (16.7%)	0	1 (4.3%)	0	0	0
Infusion site pruritus	0	0	0	1 (50.0%)	0	0
Pyrexia	0	0	0	0	1 (20.0%)	0
Body temperature increased	0	0	1 (4.3%)	0	0	0
Investigations						
ALT increased	1 (5.6%)	0	0	0	0	0
Abnormal liver test	0	0	0	0	0	1 (50.0%)
Musculoskeletal and connective tissue disorders						
Back pain	1 (5.6%)	1 (50.0%)	3 (13.0%)	0	0	0
Musculoskeletal pain	0	1 (50.0%)	1 (4.3%)	0	0	0
Nervous system disorders						
Dizziness	0	0	1 (4.3%)	0	0	0
Dysgeusia	1 (5.6%)		0	0	1 (8.3%)	0
Headache	0	0	10 (43.5%)	0	0	0
Paraesthesia	1 (5.6%)	0	0	0	0	0
Psychiatric disorders						
Anxiety	1 (5.6%)	0	2 (8.7%)	0	0	0
Respiratory, thoracic and mediastinal disorders						
dyspnoea	0	0	0	0	0	1 (50.0%)
Skin and subcutaneous						

tissue disorders						
Hyperhidrosis	0	0	0	0	1 (20.0%)	0
Blister	0	0	1 (4.3%)	0	0	0
Skin burning sensation	1 (5.6%)	0	0	0	0	0

Across all studies (both indications), the AEs that were reported more than 3 times overall were: headache (10 cases, all in haemophilia A study CSLCT-BIO-95-41; 9 cases occurred in 1 subject), back pain (5 cases, all in haemophilia A studies: 1 each in studies CSLCTBIO-07-47 and CSLCT-BIO-95-30 and 3 in study CSLCT-BIO-95-41) and tachycardia (4 cases, all in haemophilia A study CSLCT-BIO-07-47). These 4 cases of tachycardia were noted in the subject's home diary as palpitation; they were mild in intensity and resolved without any actions taken.

Serious adverse event / deaths / other significant events

Deaths

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

Serious adverse events (SAEs)

A total of 9 subjects experienced SAEs during the clinical studies, 5 subjects with haemophilia A and 4 subjects with VWD (Table 28). None of the adolescent subjects experienced an SAE. There was one event of aggravation of pre-existing FVIII inhibitors in study CSLCT-BIO-07-47 which was considered possibly related to the medication and led to discontinuation of the study for that patient (see Laboratory findings). The other SAEs were not considered related to human coagulation FVIII/VWF complex or to study procedures.

The 3-year-old child in study CSLCT-BIO-03-97 experienced an upper respiratory tract infection which was considered serious.

Table 28: Serious Adverse events in clinical trials

Preferred term	Duration (days)	Severity	Action taken	Causality (per investigator)	Outcome
Hepatic echinococciasis	29	Moderate	Dose increased	Not related	Recovered/resolved
Epstein-Barr virus infection	20	Moderate	Dose not changed	Not related	Recovered/resolved
Pneumonia mycoplasmal	12	Mild	Dose not changed	Not related	Recovered/resolved
Hypertension	16	Moderate	Dose not changed	Unlikely related	Recovered/resolved
Factor VIII inhibition	340	Moderate	Drug withdrawn	Unlikely related[b]	Recovered/resolved
Condition aggravated	340	Moderate	Drug withdrawn	Unlikely related[b]	Recovered/resolved
Study CSLCT-BIO-95-41					
Viral pericarditis	1	Severe	Corrective therapy	Not related	Resolved
Von Willebrand disease					
Study CSLCT-BIO-08-54					
Diabetes mellitus	6	Mild	None	Not related	Recovered/resolved
Study CSLCT-BIO-00-75					
Ovarian cyst ruptured	1	Severe	Not applicable	Not related	Resolved
Study CSLCT-BIO-03-97					
Myositis	29	Severe	None	Not related	Resolved
Upper respiratory tract infection	9	Moderate	None	Not related	Resolved

Laboratory findings

In the pivotal study in haemophilia A 3 of the 81 subjects in the safety population had a clinically significant value for any of the biochemistry parameters. In the supportive studies 8 subjects (3 and 5 subjects, respectively) experienced a clinically significant abnormal biochemistry result post-infusion, however, none of these values in either study were considered to be related to human coagulation FVIII/VWF complex. No clinically relevant changes in laboratory tests were reported.

FVIII inhibitors were assessed in haemophilia A studies CSLCT-BIO-07-47 and CSLCT-BIO-95- 41, as well as in VWD study CSLCT-BIO-03-97. FVIII and VWF inhibitors were assessed in VWD study CSLCT-BIO-08-54. A positive finding was reported for 1 subject in study CSLCT-BIO-07-47. The positive inhibitor titre at the final visit for this subject was also reported as an SAE that led to study discontinuation for this subject. No positive FVIII inhibitor titres occurred during haemophilia A study CSLCT-BIO-95-41 or VWD studies CSLCTBIO- 08-54 and CSLCT-BIO-03-97.

In the pivotal VWD sudy 1 subject (with hepatitis C) had clinically significant abnormal biochemistry values during the study: ALT and AST had increased from normal at baseline to abnormal at Month 3. In the supportive VWD study, 3 subjects had a clinically significant biochemistry results some of which were reported as TEAEs. Two subjects had high gamma glutamyl transferase (GGT), alkaline phosphatase (ALP), alanine transaminase (ALT) and aspartate transaminase (AST); 1 of these subjects also had high chloride and low urea with hepatic steatosis reported as a TEAE and the other subject also had a TEAE of liver function test abnormal considered possibly related to human coagulation FVIII/VWF complex. A further subject had low potassium consistent with a pre-existing hypokalaemia.

In the supportive VWD study CSLCT-BIO-03-97 one subject with abnormal liver function test was reported that was considered possibly related to human coagulation FVIII/VWF complex.

Overall, there were no consistent changes in mean biochemistry values across the studies, and no trends observed in changes in individual biochemistry values.

Safety in special populations

Intrinsic Factors

No specific subgroup analyses by intrinsic factors were conducted. Although the safety of human coagulation FVIII/VWF complex has not been systematically evaluated in children yet, currently available clinical experience (including the Howman study) and post-marketing information suggest no apparent differences in children compared to adults. 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.

Safety in Adolescent Subjects

Eight adolescent subjects (aged 12 - <18 years) were included in the prospective clinical studies, 5 in haemophilia A studies (3 in study CSLCT-BIO-07-47 and 2 in study CSLCT-BIO-95-41; 1 of the latter 2 also participated in study CSLCT-BIO-95-30) and 3 in VWD study CSLCT-BIO-08- 54.

No TEAEs occurred in the 3 adolescent subjects that participated in pivotal haemophilia A study CSLCT-BIO-07-47. One of the 2 adolescents in supportive haemophilia A study CSLCT-BIO-95-41 experienced 1 TEAEs during the study: 1 subject reported a skin laceration, which was considered unrelated to the IMP by the investigator. Another subject participating in both studies CSLCT-BIO-95-30 and CSLCT-BIO-95-41 did not experience any TEAEs. Six TEAEs occurred in 1 of the 3 adolescent subjects that participated in the pivotal VWD study CSLCT-BIO-08-54: 1 subject experienced 3 cases of headache (2 moderate, 1 mild) and 1 case each of abdominal pain (moderate), sneezing (moderate), and cervix disorder (mild). All these events were considered unrelated to the IMP. All events resolved within 1 day with the exception of the cervix disorder which was still ongoing at the time of the interim database lock. Neither of the other 2 adolescent subjects experienced a TEAE.

One case of nausea, which was considered possibly related to the IMP by the investigator, was reported in the Howman study in one subject. No clinically relevant findings were noted in adolescent subjects in any of the other safety assessments.

Safety in Children

One child (<12 years) was included in the prospective clinical studies: in supportive VWD study CSLCT-BIO-03-97, a 3-year-old child with Type 3 VWD was enrolled and received prophylactic treatment with human coagulation FVIII/VWF complex. The child experienced 6 TEAEs during the study: catheter-related infection, pyrexia, oropharyngeal pain, headache, rhinorrhoea, and upper respiratory tract infection. All these events were mild or moderate in intensity, considered not related to the IMP, and

resolved without changing the study medication regimen. The upper respiratory tract infection was considered serious.

No AEs occurred in children (aged <12 years) that participated in the Howman study.

Use in Pregnancy and Lactation

No safety data concerning the use of human coagulation FVIII/VWF complex during pregnancy and lactation are available.

Safety related to drug-drug interactions and other interactions

No interactions between human coagulation FVIII/VWF complex and other medicinal products have been observed.

Discontinuation due to adverse events

Overall, 2 subjects discontinued study participation due to a TEAE. In addition to one subject in study CSLCT-BIO-07-47 who discontinued the study due to aggravation of pre-existing FVIII inhibitors (reported as SAE), 1 subject in the supportive haemophilia A study CSLCT-BIO-95-41 withdrew due to recurrent episodes of chest pain, back pain, and anxiety occurring 3-5 minutes post-infusion. The subject received a total of 10 infusions of human coagulation FVIII/VWF complex, but the above described AEs occurred after the last 2 infusions. The events were mild, resolved without sequelae, and were considered by the investigator to be related to the IMP. The subject had experienced similar TEAEs (back pain and musculoskeletal pain) in the preceding PK study CSLCT-BIO-95-30.

Post marketing experience

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). However, first supply of human coagulation FVIII/VWF complex (Voncento) to patients occurred in 2001 in Singapore.

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, 2010 [paediatric subjects only]) and data from the Australian Adverse Drug Reactions Advisory Committee database. The Periodic Safety Update Reports (PSURs) written for human coagulation FVIII/VWF complex were provided along with a cumulative line listing of all spontaneous reports received since registration.

Human coagulation FVIII/VWF complex was first registered in Australia in August 2000 and has since been registered in 11 other countries (New Zealand, Singapore, Hong Kong, Malaysia, Guatemala, El Salvador, Taiwan, Peru, Chile, Brazil, and Colombia), as Voncento, Aleviate, Human Coagulation Factor VIII, or TBSF Human Factor VIII. The indications covered include treatment and prophylaxis of bleeding events in patients with FVIII deficiency due to haemophilia A and in patients with VWD for whom treatment with DDAVP is ineffective or contraindicated. In Australia, New Zealand, and Brazil both indications are registered, while in the other countries, only the indication haemophilia A is registered.

Since launch of human coagulation FVIII/VWF complex and up to April 2011, 1,305,190 vials were distributed globally, and on average, 2.1 AE reports per every 100,000 vials or 2.5 spontaneous cases per year have been reported (Table 29).

Table 29: Post-marketing adverse events reported per 100,000 vials of human coagulation FVIII/VWF complex between 2000 and April 2011

Year of PSUR [a]	Total AE Reports	No. of vials distributed	AE reports per 100,000 vials
2000	0	0	0
2001	0	827	0
2002	0	6,841	0
2003	11	142,646	7.7
2004	9	187,246	4.8
2005	0	96,898	0
2006	3	113,252	2.6
2007	1	122,767	0.8
2008	1	222,558	0.4
2009	0	136,258	0
2010	0	139,270	0
2011 [b]	2	136,627	1.5
Total	**27**	**1,305,190**	**2.1**

AE = adverse event; PSUR = periodic safety update report.

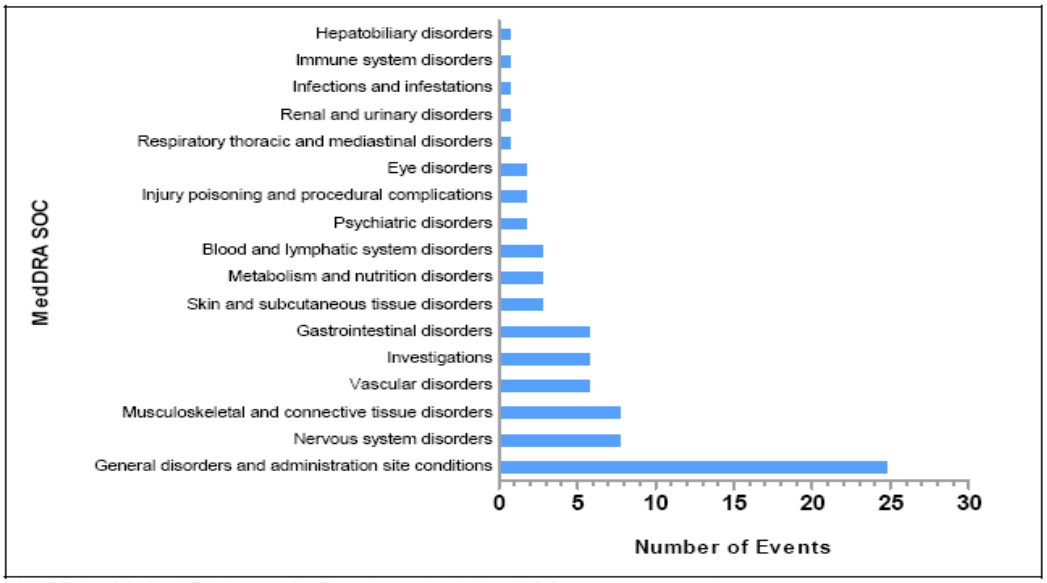
[a] in August of each year with the exception of 2000-2002 where no formal PSURs were issued, as agreed in communication with the Australian Therapeutic Goods Administration.

[b] up to end of April 2011 (data summarised in a line listing).

Since August 2000, 27 spontaneous cases, including a total of 79 events reported for human coagulation FVIII/VWF complex, have been entered into CSL's worldwide safety database. Twenty-four of these reports were from health care professionals and 3 reports were identified in the worldwide literature. All these spontaneous reports were considered to be reactions to human coagulation FVIII/VWF complex. However, not all reactions were categorised as expected events. Twenty-three of these reports were classified as non-serious, while 4 reports contained at least 1 serious event.

Frequencies of the total of 79 reported events are depicted by MedDRA system organ class SOC in Figure 5. The largest proportion of events (25 events [32%]) is from the general disorders and site administration conditions SOC. Next most commonly affected SOCs are nervous system disorders and musculoskeletal and connective tissue disorders, with 8 events (10%) each.

Figure 5: Post-marketing adverse events per MedDRA system organ class



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

The MedDRA preferred terms that were reported in each SOC are listed in Table 30. The 79 events comprised 40 different preferred terms.

Table 30: Post-marketing adverse events reported from launch to April 2011

MedDRA Standard System Organ Class	MedDRA Preferred Term
Respiratory thoracic and mediastinal disorders	Sneezing
Renal and urinary disorders	Renal failure acute
Infections and infestations	Sepsis
Immune system disorders	Seasonal allergy
Hepato-biliary disorders	Hepatitis
Psychiatric disorders	Anxiety, panic reaction
Eye disorders	Eye swelling, lacrimation increased
Skin and subcutaneous tissue disorders	Rash pruritic, rash macular, hyperhidrosis
Injury, poisoning and procedural complications	Underdose
Metabolism and nutrition disorders	Decreased appetite
Blood and lymphatic system disorders	Coagulopathy, Factor VIII inhibition
Vascular disorders	Hypotension, flushing, pallor,
Investigations	Pulse absent, blood pressure increased, blood pressure decreased, hepatic enzyme increased, drug half-life reduced
Gastrointestinal disorders	Nausea, vomiting
Nervous system disorders	Tremor, dizziness
Musculoskeletal and connective tissue disorders	Muscle twitching, back pain, neck pain, arthralgia
General disorders and administration site conditions	Catheter site pain, pyrexia, malaise, chills, feeling of body temperature change, chest discomfort, chest pain, drug ineffective.

MedDRA = Medicinal Dictionary for Regulatory Activities.

All of the reported 79 events received medical review at CSL where the clinical circumstances were assessed against the reference safety information. No changes to the reference safety information were deemed necessary from the evaluation of these events.

The age distribution among the 27 spontaneous cases varied: 5 cases (19%) involved patients >45 years of age; 10 cases (37%) involved patients aged 18-45 years; 1 case (4%) was from a child and 1 case from an adolescent (aged 12 - <18 years). For 10 cases (37%), the age of the patient was not specified.

The risks associated with the use of human coagulation FVIII/VWF complex in patients with haemophilia A and VWD are those associated with the use of any plasma-derived coagulation factors. These include viral transmission, inhibitor formation and related immunomodulatory effects, allergic/anaphylactic reactions, and thrombosis.

• Viral transmission: The reference safety information acknowledges that despite the safety measures included in the manufacturing process for human coagulation FVIII/VWF complex (virus removal and inactivation) such products may still potentially transmit disease. There is also the possibility that other known or unknown infectious agents may be present. To date there have been no clinical data to support the occurrence of viral transmission following the administration of human coagulation FVIII/VWF complex. The preferred term of hepatitis was an acute flare of pre-existing hepatitis and not a new case of hepatitis after human coagulation FVIII/VWF complex infusion.

• Inhibitor formation and related immunomodulatory effects: The reference safety information for human coagulation FVIII/VWF complex states that the formation of neutralising antibodies (inhibitors) to FVIII is a known complication in the management of individuals with haemophilia A (see SmPC section 4.3). This risk correlates with the exposure to FVIII and is highest within the first 20 exposure days. Rarely inhibitors may develop after the first 100 exposure days. To date, 2 cases of inhibitor formation to human coagulation FVIII/VWF complex were reported to CSL after 10 years of post-marketing surveillance:

In addition, 8 of the 27 spontaneous cases received during post-marketing surveillance were from the same reporter in Singapore describing 8 patients who did not adequately respond to human coagulation FVIII/VWF complex (lack of efficacy). A single batch of human coagulation FVIII/VWF complex was involved; however, a batch investigation did not reveal any possible cause of the AE, and it was concluded that there was no batch-specific reason for these reports. No further information was retrieved and no evidence of inhibitor formation was confirmed. No knowledge of the circumstances of administration or use was obtained.

CSL has conducted enhanced post-marketing surveillance in Australia to investigate the incidence of inhibitor development in patients with haemophilia A following addition of prion filtration in the manufacturing process in 2007. This surveillance included the monitoring of the dosing provided to 31 patients over 6 months and an additional informal telephone and email survey for a further 6 months. No inhibitor development was identified.

• Allergic/anaphylactic reactions: To date, there have been no reports of anaphylactic reactions following the administration of human coagulation FVIII/VWF complex received. However, as with any intravenous protein product, allergic type hypersensitivity reactions are possible and symptoms indicative for such reactions were observed.

• Thrombosis: Thromboembolic events have been rarely reported in patients with VWD receiving coagulation factor replacement therapy. There is a theoretical possibility that supranormal levels of FVIII:C may increase the risk-factors for VTE. To date, there have been no post-market spontaneous reports of thromboembolic type events (including deep vein thrombosis or pulmonary embolism) after treatment with human coagulation FVIII/VWF complex.

2.6.1. Discussion on clinical safety

The most common AEs reported and related to Voncento (both indications) were: FVIII inhibition, VWF inhibition, liver function test abnormal, hypersensitivity (including tachycardia, chest pain, chest discomfort and back pain), dysgeusia, thromboembolic event, pyrexia and headache.

Across all studies (both indications), the only AEs that were reported more than 3 times overall were: headache, back pain and palpitations. The AEs were mild to moderate and resolved spontaneously.

Nine SAEs were reported, 8 were related to study procedures and one event of aggravation of pre-existing FVIII inhibitors was considered related to the medication and led to discontinuation. No deaths, no viral transmission and no allergic reactions occurred.

Overall, 2 subjects discontinued the medication due to a TEAE (possibly related to Voncento). One due to aggravation of pre-existing FVIII inhibitors and the other subject discontinued the study due to recurrent episodes of chest pain, back pain, and anxiety occurring 3-5 minutes post-infusion.

Hypersensitivity (allergic reactions): Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest (including chest pain and chest discomfort), back pain, tingling, vomiting, wheezing) have been observed, and may in some cases progress to severe anaphylaxis (including shock) (see SmPC section 4.8).

FVIII inhibition: Patients with haemophilia A may develop neutralising antibodies (inhibitors) to FVIII. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted. There is no experience from clinical trials with Voncento in previously untreated patients (PUPs). Therefore, no valid figures on the incidence of clinically relevant specific inhibitors are currently available (see SmPC section 4.8).

VWF inhibition: Patients with VWD, especially type 3 patients, may develop neutralising antibodies (inhibitors) to VWF. If such inhibitors occur, the condition will manifest itself as an inadequate clinical response. Such antibodies are precipitating and may occur concomitantly to anaphylactic reactions. Therefore, patients experiencing an anaphylactic reaction should be evaluated for the presence of an inhibitor. In all such cases, it is recommended that a specialised haemophilia centre be contacted (see SmPC section 4.8).

Thromboembolic events: In patients with VWD, there is a risk of occurrence of thromboembolic events, particularly in patients with known clinical or laboratory risk factors. In patients receiving FVIII-containing VWF products, sustained excessive FVIII:C plasma levels may increase the risk of thromboembolic events. Therefore, patients at risk must be monitored for early signs of thrombosis. Prophylaxis against venous thromboembolism should be instituted, according to the current recommendations (see SmPC sections 4.3 and 4.4).

All the adverse reactions from the safety database reported in clinical trials and post-marketing have been included in the SmPC.

One case of overdose has been reported from clinical trials. No undesirable effects were associated with this overdose. The risk of thromboembolic events cannot be excluded in case of major overdose, especially in patients with VWD (see SmPC section 4.9).

Experience in the treatment of pregnant or lactating women is not available. There are no data on fertility available. Voncento should be administered to pregnant or lactating VWF deficient women only if clearly indicated, taking into consideration that delivery confers an increased risk of haemorrhagic events in these patients. Based on the rare occurrence of haemophilia A in women, experience regarding the

treatment during pregnancy and breastfeeding is not available. Therefore, Voncento should be used during pregnancy and lactation only if clearly indicated (see SmPC section 4.6).

Voncento has no influence on the ability to drive and use machines (see SmPC section 4.7).

There are insufficient data to estimate the frequency, type and severity of adverse reactions of Voncento in the paediatric population (see SmPC section 4.8).

There is insufficient information to estimate the frequency, type and severity of adverse reactions of Voncento in the population older than 65 years (see SmPC section 4.8).

2.6.2. Conclusions on the clinical safety

The safety profile of Voncento is considered acceptable. The AEs seen were mild-moderate and do not influence the safety profile. The incidence of SAEs reported is low and the type of adverse events reported is expected for this product.

Inhibitor formation was seen in one subject with haemophilia. The time frame and amount of subjects studied is not sufficient to draw definite conclusions for this specific adverse event. Therefore post-marketing studies in patients with haemophilia A and in patients with VWD are considered to be necessary and the Applicant committed to perform the required post-marketing studies in both indications which will provide additional safety data.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

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

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 2, the PRAC considers by consensus that the risk management system for human plasma-derived Von Willebrand factor and human coagulation factor VIII in the treatment of the proposed indications

- *von Willebrand disease (VWD): Treatment of haemorrhage or prevention and treatment of surgical bleeding in patients with VWD, when desmopressin (DDAVP) treatment alone is ineffective or contraindicated.*
- *Haemophilia A (congenital FVIII deficiency): Prophylaxis and treatment of bleeding in patients with haemophilia A.*

could be acceptable provided an updated risk management plan is submitted implementing the following changes:

- The proposed post-marketing safety and efficacy study in VWD is considered acceptable *if the applicant commits to enrol at least (and not 'approximately') 20 patients that have not yet been included in any of the studies with Voncento/Biostate* before.
- Amendments to the targeted questionnaires following receipt of case reports of Inhibitor development, Embolic and thrombotic events, Transmission of infectious agents (to be agreed upon with the Regulatory Authorities before launch in the EU).

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

  The applicant identified the following safety concerns in the RMP:

  Table 31: Summary of the Safety Concerns

Important identified risks	• Development of FVIII/VWF inhibitors • Embolic and thrombotic events • Hypersensitivity reactions, including anaphylaxis • Lack of Drug Effect
Important potential risks	• Transmission of infectious agents • Off-label use including in ITI therapy and children under 12 years • Medication Error • Safety in the home therapy setting, including risk of errors in handling and maladministration
Important missing information	• Paediatric data (<12 years) • Patients with a current or known history of an inhibitor to FVIII or VWF • Treatment and inhibitor formation in PUPs • Mild forms of haemophilia A • Pregnant or lactating women • Elderly patients above 65 years of age • Patients with AIDS or other chronic illness • Immune Tolerance Induction data • Exposure data in non-Caucasian ethnic groups

  The PRAC agreed with the identified safety concerns by the applicant.

- **Pharmacovigilance plan.**

- **Table 32: Summary of routine and additional Pharmacovigilance activities**

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)
Important identified risks	
Development of FVIII/VWF inhibitors	Routine Pharmacovigilance including additional follow-up and target questionnaire. Review of available safety data (including the ongoing VWD extension study CSLCT-BIO-09-64 and post-marketing active surveillance) at 6 month milestones in PSUR Review of available safety data from the PMS studies CSLCT-BIO-12-78 and CSLCT-BIO-12-83 A comprehensive analysis of reported de novo and recurrent inhibitors, provided as a cumulative report in the initial RMP and all subsequent updates
Important identified risks	
Embolic and thrombotic events	Routine Pharmacovigilance including additional follow-up and target questionnaire. Review of available safety data (including the ongoing VWD extension study CSLCT-BIO-09-64 and post-marketing active surveillance) at 6 month milestones in PSUR. Review of available safety data from the PMS studies CSLCT-BIO-12-78 and CSLCT-BIO-12-83
Hypersensitivity reactions, including anaphylaxis	Routine Pharmacovigilance including additional follow-up and target questionnaire. Review of available safety data (including the ongoing VWD extension study CSLCT-BIO-09-64 and post-marketing active surveillance) at 6 month milestones in PSUR Review of available safety data from the PMS studies CSLCT-BIO-12-78 and CSLCT-BIO-12-83
Lack of Drug Effect	Routine Pharmacovigilance Review of available safety data (including the ongoing VWD extension study CSLCT-BIO-09-64 and post-marketing active surveillance) at 6 month milestones in PSUR Review of available safety data from the PMS studies CSLCT-BIO-12-78 and CSLCT-BIO-12-83
Important potential risks	
Transmission of infectious agents	Routine Pharmacovigilance including additional follow-up and target questionnaire. Review of available safety data (including the ongoing VWD extension study CSLCT-BIO-09-64 and post-marketing active surveillance) at 6 month milestones in PSUR Review of available safety data from the PMS studies CSLCT-BIO-12-78 and CSLCT-BIO-12-83
Off-label use, including in ITI therapy and children under 12 years	Routine Pharmacovigilance Review of available safety data at 6 month milestones in PSUR
Safety Concern	**Proposed Pharmacovigilance Activities (routine and additional)**
Medication Errors	Routine Pharmacovigilance Review of available safety data (including the ongoing VWD extension study CSLCT-BIO-09-64) at 6 month milestones in PSUR Review of available safety data from the PMS studies CSLCT-BIO-12-78 and CSLCT-BIO-12-83
Safety in the Home Therapy Setting, including Risk of Error in Handling and Maladministration	Routine Pharmacovigilance Review of available safety data (including the ongoing VWD extension study CSLCT-BIO-09-64) at 6 month milestones in PSUR Review of available safety data from the PMS studies

	CSLCT-BIO-12-78 and CSLCT-BIO-12-83
Important missing information	
Paediatric data (< 12 years)	Paediatric clinical studies in haemophilia A and VWD (in patients 0-<12 years of age) have been started according to the approved PIP. •CSLCT-BIO-08-53 •CSLCT-BIO-08-52 Review of available safety data (including the ongoing VWD extension study CSLCT-BIO-09-64) at 6 month milestones in PSUR
Patients with a current or known history of an inhibitor to FVIII or VWF	Routine Pharmacovigilance Review of available safety data at 6 month milestones in PSUR
Treatment and inhibitor formation in PUPs	Routine Pharmacovigilance including additional follow-up and target questionnaire. Review of available safety data at 6 month milestones in PSUR
Mild forms of haemophilia A	Routine Pharmacovigilance Review of available safety data at 6 month milestones in PSUR
Pregnant or lactating women	Routine Pharmacovigilance Review of available safety data at 6 month milestones in PSUR
Elderly patients above 65 years of age	Routine Pharmacovigilance Review of available safety data (including the ongoing VWD extension study CSLCT-BIO-09-64) at 6 month milestones in PSUR Review of available safety data from the PMS studies CSLCT-BIO-12-78 and CSLCT-BIO-12-83
Patients with AIDS or other chronic illness	Routine Pharmacovigilance Review of available safety data at 6 month milestones in PSUR Review of available safety data from the PMS studies CSLCT-BIO-12-78 and CSLCT-BIO-12-83
Immune Tolerance Induction data	An ITI clinical study in 20 patients (to obtain 15 evaluable) has been started according to the approved PIP. • CSLCT-BIO-10-67 Review of available safety data (including a retrospective non-interventional review) at 6 month milestones in PSUR
Exposure data in non-Caucasian ethnic groups	Routine Pharmacovigilance Review of available safety data at 6 month milestones in PSUR Review of available safety data from the PMS studies CSLCT-BIO-12-78 and CSLCT-BIO-12-83

- **Risk minimisation measures**

Table 33: Summary table of Risk Minimisation Measures

Safety Concern	**Routine risk minimisation activities sufficient?**	**If yes, provide description of routine activity and justification**
Important identified risks		
Development of FVIII/VWF inhibitors	Yes	Can be managed by routine labelling, including statements in special warning and precautions for use section of SmPC to inform health professionals of the risk of development of FVIII/VWF inhibitors: Haemophilia A: The formation of neutralising

		antibodies (inhibitors) to FVIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the FVIII procoagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma. The risk of developing inhibitors is correlated to the exposure to factor FVIII, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days. Cases of recurrent inhibitor (low titre) have been observed after switching from one factor VIII product to another in previously untreated patients with more than 100 exposure days who have a previous history of inhibitor development. Therefore, it is recommended to monitor all patients carefully for inhibitor occurrence following any product switch. In general, all patients treated with human coagulation FVIII should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for FVIII inhibitor presence should be performed. In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered. The management of such patients should be directed by physicians with experience in the care of haemophilia A patients and those with factor VIII inhibitors. VWD: Patients with VWD, especially type 3 patients, may develop neutralising antibodies (inhibitors) to VWF. If the expected VWF:RCo activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, an appropriate assay should be performed to determine if a VWF inhibitor is present. In patients with high levels of inhibitor, therapy may not only be ineffective but also lead to anaphylactoid reactions and other therapeutic options should be considered. Statements on the development of FVIII/VWF inhibitors are also found in the undesirable effects sections of SmPC. PMS studies CSLCT-BIO-12-78 and CSLCT-BIO-12-83 will collect long-term data on: •The incidence of Factor VIII (FVIII) and VWF inhibitors

Embolic and thrombotic events	Yes	Can be managed by routine labelling, including statements in special warning and precautions for use section of SmPC to inform health professionals of the risk of embolic and thrombotic events: VWD: There is a risk of occurrence of thrombotic events, particularly in patients with known clinical or laboratory risk factors. Therefore, patients at risk must be monitored for early signs of thrombosis. Prophylaxis against venous thromboembolism should be instituted, according to the current recommendations. When using a FVIII-containing VWF product, the treating physician should be aware that continued treatment may cause an excessive rise in FVIII:C. In patients receiving FVIII-containing VWF products, plasma levels of FVIII:C should be monitored to avoid sustained excessive FVIII:C plasma levels which may increase the risk of thrombotic events, and antithrombotic measures should be considered. Statements on embolic and thrombotic events are also found in the undesirable effects and overdose sections of SmPC. PMS studies CSLCT-BIO-12-78 and CSLCT-BIO-12-83 will collect long-term data on: The safety of Voncento in subjects with haemophilia A and VWD.
Hypersensitivity reactions, including anaphylaxis	Yes	Can be managed by routine labelling, including statements in special warning and precautions for use section of SmPC to inform health professionals of the risk of hypersensitivity reactions, including anaphylaxis: “Allergic type hypersensitivity reactions are possible. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the medicinal product immediately and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. In case of shock, the current medical standards for shock treatment should be observed.” Statements on hypersensitivity reactions (including anaphylaxis) are also found in the undesirable effects and contraindications sections of SmPC. PMS studies CSLCT-BIO-12-78 and CSLCT-BIO-12-83 will collect long-term data on: The safety of Voncento in subjects with haemophilia A and VWD.
Lack of Drug Effect	Yes	Can be managed by routine labelling, including statements in the SmPC to inform health professionals of the risk of lack of drug effect. As lack of drug effect is most often associated with the development of inhibitory antibodies, refer to statements from SmPC described above under Important Identified Risk: Development of FVIII/VWF inhibitors. PMS studies CSLCT-BIO-12-78 and CSLCT-BIO-12-83 will collect long-term data on: The safety of Voncento in subjects with haemophilia A and VWD.
Important potential risks		

Transmission of infectious agents	Yes	Can be managed by routine labelling, including statements in special warning and precautions for use section of SmPC to inform health professionals of the risk of transmission of infectious agents: Virus safety: Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV, and for the non-enveloped virus HAV. The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (foetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia). Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of human plasma-derived products. It is strongly recommended that every time that Voncento is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product. PMS studies CSLCT-BIO-12-78 and CSLCT-BIO-12-83 will collect long-term data on: The safety of Voncento in subjects with haemophilia A and VWD.
Off-label use, including in ITI therapy and children under 12 years	Yes	Product indications will be limited to adolescent and adult populations (≥12 years), and will not include use in ITI at initial submission. Can be managed by routine labelling, including statements in therapeutic indications section of SmPC to inform health professionals of labeled indications: VWD: Treatment of haemorrhage or prevention and treatment of surgical bleeding in patients with VWD, when desmopressin (DDAVP) treatment alone is ineffective or contraindicated. Voncento is indicated in patients 12 years and older. Haemophilia A: Prophylaxis and treatment of bleeding in patients with haemophilia A. Voncento is indicated in patients 12 years and older.

Medication Error	Yes	Can be managed by routine labelling, including extensive instructions to inform health professionals of reconstitution, dosage and administration of product, in the posology and method of administration and special precautions for disposal and other handling sections of SmPC. Statements in the overdose section of SmPC include: One case of overdose has been reported from clinical trials. No undesirable effects were associated with this overdose. Additionally, the outer labelling (carton and label) displays both the FVIII and VWF content, and uses different colour design for each strength. Statements on carton and label include: Read the package leaflet before use. PMS studies CSLCT-BIO-12-78 and CSLCT-BIO-12-83 will collect long-term data on: The safety of Voncento in subjects with haemophilia A and VWD.
Safety in the home therapy setting, including risk of errors in handling and maladministration	Yes	Can be managed by routine labelling, including statements in posology and method of administration section of SmPC to inform health professionals on safety in the home therapy setting: Treatment of VWD and haemophilia A should be supervised by a physician experienced in the treatment of haemostatic disorders. The decision on the use of home treatment for an individual patient should be made by the treating physician who should ensure that appropriate training is provided and the use is reviewed at regular intervals Additionally, the Package Leaflet includes extensive instructions to inform patients of reconstitution, dosage and usage of product. PMS studies CSLCT-BIO-12-78 and CSLCT-BIO-12-83 will collect long-term data on: The safety of Voncento in subjects with haemophilia A and VWD.
Important missing information		
Paediatric data (< 12 years)	Yes	Product indications will be limited to adolescent and adult populations (≥12 years) at initial submission. Can be managed by routine labelling, including statements in therapeutic indications section of SmPC to inform health professionals of labeled indications: Voncento is indicated in patients 12 years and older.
Patients with a current or known history of an inhibitor to FVIII or VWF	Yes	Can be managed by routine labelling, including statements in special warning and precautions for use; posology and method of administration; and undesirable effects sections of SmPC to inform health professionals of usage in patients with a current or known history of an inhibitor to FVIII or VWF; as discussed above under Identified Risk: Development of FVIII/VWF inhibitors.

Treatment and inhibitor formation in PUPs	Yes	Can be managed by routine labelling, including statements in special warning and precautions for use; posology and method of administration; and undesirable effects sections of SmPC to inform health professionals of treatment and inhibitor formation in PUPs; as discussed above under Important Identified Risks: Development of FVIII/VWF inhibitors.
Mild forms of haemophilia A	Yes	Can be managed by routine pharmacovigilance activities. Haemophilia A: prophylaxis and treatment of bleeding in patients with haemophilia A.
Pregnant or lactating women	Yes	Can be managed by routine labelling, including statements in fertility, pregnancy and lactation section of SmPC to inform health professionals of usage in pregnant or lactating women: Animal reproduction studies have not been conducted with Voncento . <u>Von Willebrand disease</u> Experience in the treatment of pregnant or lactating women is not available. Voncento should be administered to pregnant or lactating VWF deficient women only if clearly indicated, taking into consideration that delivery confers an increased risk of haemorrhagic events in these patients. <u>Haemophilia A</u> Based on the rare occurrence of haemophilia A in women, experience regarding the treatment during pregnancy and breastfeeding is not available. Therefore, Voncento should be used during pregnancy and lactation only if clearly indicated. <u>Fertility</u> There are no data on fertility available.
Important missing information		
Elderly patients above 65 years of age	Yes	Can be managed by routine labelling, including statements in posology and method of administration section of SmPC to inform health professionals of usage in elderly patients: No dosage adjustment is necessary for the older people. PMS studies CSLCT-BIO-12-78 and CSLCT-BIO-12-83 will collect long-term data on: The safety of Voncento in subjects with haemophilia A and VWD.
Patients with AIDS or other chronic illness	Yes	Can be managed by routine pharmacovigilance activities. PMS studies CSLCT-BIO-12-78 and CSLCT-BIO-12-83 will collect long-term data on: The safety of Voncento in subjects with haemophilia A and VWD.

Immune Tolerance Induction data	Yes	Product indications will not include use in ITI at initial submission. Can be managed by routine labelling, including statements in therapeutic indications section of SmPC to inform health professionals of labelled indications:: VWD: Treatment of haemorrhage or prevention and treatment of surgical bleeding in patients with VWD, when desmopressin (DDAVP) treatment alone is ineffective or contraindicated. Haemophilia A: Prophylaxis and treatment of bleeding in patients with haemophilia A.
Exposure data in non-Caucasian ethnic groups	Yes	Can be managed by routine pharmacovigilance. PMS studies CSLCT-BIO-12-78 and CSLCT-BIO-12-83 will collect long-term data on: The safety of Voncento in subjects with haemophilia A and VWD.

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications.

The applicant submitted version 3.0 of the RMP implementing the changes proposed by the PRAC:

- Amendment to the post-marketing safety and efficacy study in VWD anticipating *to enrol <u>at least</u> (and not 'approximately') 20 patients that have <u>not</u> yet been included in any of the studies with Voncento/Biostate* before. Following the opinion by the CHMP, the applicant will submit full study protocols for the PMSs in haemophilia A and in VWD (to be submitted by 31 August 2013), which also will be included in the next update of the RMP.
- Amendments to the targeted questionnaires on Inhibitor development, Embolic and thrombotic events, Transmission of infectious agents. These questionnaires will be agreed upon with the Regulatory Authorities before launch in the EU.

The CHMP endorsed this advice with further changes requested for the next revision of the RMP in order to reflect the therapeutic indications, as agreed by CHMP. These changes concerned the following elements of the Risk Management Plan:

Safety concerns and proposed Pharmacovigilance Activities; Risk Minimisation measures; Data in paediatric patients < 12 years.

The CHMP justified these changes as follows:

Following consultation with the BPWP on the requirements for inclusion of children < 12 years in the post-marketing studies for both indications:

- A two-step approach is recommended for the requirements for paediatric data in VWD patients. The first-step is the submission and evaluation of the final clinical study report (CSLCT-BIO-08-52) investigating 8 paediatric patients < 12 years in 2014. Once these data are available and provided the evaluation is positive, the post-marketing study >12 years (CSLCT-BIO-12-83) should be opened to allow enrolment of patients < 12 years. The company's agreement to this strategy should be reflected in the Risk Management Plan. (The current VWF products on the market are plasma-derived and, therefore, the fact that this is a plasma-derived product does not create the difficulties in recruitment of children seen with plasma-derived FVIII products.)"
- Regarding haemophilia A:"… the company should make efforts to collect more data in order to get closer to the guideline recommendation and, therefore, the data from the on-going paediatric study should be supplemented with paediatric data collected in the post-authorisation phase,

following the same step-wise approach as described above for VWD. Therefore, once the data are available from paediatric study (CSLCT-BIO-08-53) and provided the evaluation is positive, the post-marketing study >12 years (CSLCT-BIO-12-78) should be opened to allow enrolment of patients < 12 years. The company's agreement to this strategy should be reflected in the Risk Management Plan. In this context, it was noted that while data in immune tolerance induction (ITI) is also of interest, it will not contribute to the evaluation of immunogenicity, which is the main purpose of the post-authorisation study recommended in the FVIII guideline."

It is noted that the applicant agreed to open the patient enrolment to patients < 12 years in the post-marketing studies for haemophilia A and VWD as requested by CHMP. The applicant further agreed to implement this in the full PMS study protocols for both indications (to be submitted by 31 August 2013) which, as stated above, will also be included in the next update of the RMP.

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Von Willebrand Disease

In the pivotal Study CSLCT-BIO-08-54 efficacy in the on-demand treatment of non-surgical bleeds, studied in 20 subjects for 12 months, was reported by the investigator as being excellent in 371/405 (91.6%) of the bleeds, good in 27/405 (6.7%) and moderate in 7/405 (1,7%). These bleeds included 7 major mucosal bleeds as required by the relevant CHMP guideline. The subject's assessment of hemostatic efficacy per day of bleeding event on all bleeding days was excellent in 476/602 (79.1%), good in 104/602 (17.3%), moderate in 21/602 (3.5%).

In Study CSLCT-BIO-03-97, Biostate was used in 10 major surgeries in 9 patients and in 15 minor surgeries in 11 patients. In those surgeries, where hemostatic efficacy was reported, efficacy was rated on day 1 as excellent in 10/11 of the minor surgeries and in 8/10 of the major surgeries, and as good in the other 2 major surgeries and 1 minor surgery.

Hemophilia A

In the pivotal Study CSLCT-BIO-07-47, in the prophylaxis subgroup, the mean (± s.d) number of bleeds overall was 3.5 ± 4.7 (n = 29). In the prevention subgroup, the mean (± s.d) number of bleeds overall was 10.7 ± 10.3 (n = 51). Eleven subjects in the prophylaxis subgroup and 6 subjects in the prevention subgroup had no bleeding events during the study. The median number of bleeds per month in the first month was 0 in the prophylaxis sub-group (range 0 to 5) and 1 in the prevention sub-group (range 0 to 8) and values were almost the same in the following months.

There was an Investigator's assessment of hemostatic efficacy assessment in 656 of the 667 reported bleeding events which was excellent in 396/656 (60.4%); good in 236/656 (36.0%); moderate in 23/656(3.5%). The pattern of efficacy was similar in the prophylaxis and prevention subgroups.

A total of 37 surgical procedures, of which 12 were major were performed in 20 subjects of the efficacy population. 10 major surgeries in 10 subjects and 10 minor surgeries in 3 subjects fulfilled the

requirements of the previous and current FVIII guidelines. At discharge, the Investigator assessed the hemostatic efficacy for 2 of the major surgical events as good and for the remaining major and minor surgical events as excellent.

Because high purity plasma derived FVIII or recombinant FVIII concentrates are readily available, products containing a large amount of VWF are not routinely used in patients with hemophilia A and are of limited relevance in standard treatment.

However, there may be a place for FVIII concentrates containing VWF in immune tolerance induction (ITI) regimens and for use in this clinical situation it is relevant that efficacy in hemophilia A patients has been demonstrated.

Uncertainty in the knowledge about the beneficial effects.

There are minimal paediatric data in patients with Von Willebrand Disease and Hemophilia A.

The CHMP agreed on the requirements for a stepwise inclusion of children in the post-marketing studies for both indications:

The submission and evaluation of the final clinical study report (CSLCT-BIO-08-52) investigating 8 paediatric patients < 12 years is planned for 2014 – also as part of the ongoing PIP. Once these data are available and provided the evaluation is positive, the post-marketing study >12 years (CSLCT-BIO-12-83) will be opened to allow enrolment of patients < 12 years.

The applicant will follow the same step-wise approach for Hemophilia A as described above for VWD. Therefore, once the data are available from paediatric study (CSLCT-BIO-08-53) and provided the evaluation is positive, the post-marketing study >12 years (CSLCT-BIO-12-78) will be opened to allow enrolment of patients < 12 years.

This strategy will be reflected in the Risk Management Plan. In this context, it was noted that while data in immune tolerance induction (ITI) is also of interest, it will not contribute to the evaluation of immunogenicity, which is the main purpose of the post-authorisation study recommended in the FVIII guideline.

Risks

Unfavourable effects

No major risks were seen or unexpected AE's reported. Most AEs were mild-moderate. The incidence of SAEs reported is low and the type of AE might be as expected for this product. The most common AEs reported that were related to Voncento, were: headache, arthralgia, back pain and nausea. Across all studies AEs that were reported more than 3 times were: headache, back pain and palpitations.

The high levels of FVIII seen in surgery study CSLCT-BIO-03-97 carry a risk of thrombosis and one case of thrombophlebitis was seen in a patient with a FVIII:C > 200% in that study. However, this is a recognized risk of treatment of VWD patients with products containing both FVIII and VWF, especially during surgery and is addressed in the core SPC for VWF concentrates. It can be managed by monitoring plasma FVIII levels and if necessary by changing the dosage regimen or by changing to a product with a lower FVIII content.

Two subjects discontinued the medication due to a TEAE (events related to Voncento): one due to aggravation of pre-existing FVIII inhibitor (Hemophilia A study CSLCT-BIO-07-47) and the other discontinued the study due to recurrent episodes of chest pain, back pain, and anxiety occurring 3-5 minutes post-infusion. No drug-drug interaction, deaths, thromboembolic events or allergic reaction were reported.

No positive FVIII or VWF inhibitor titers occurred during the pivotal VWD studies.

In the retrospective investigator-led Howman study, 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.

In Study CSLCT-BIO-03-97, very high pre-treatment (trough) levels of FVIII:C were seen in some patients with in 2 cases levels above the reference upper limit of 200%. These were trough levels from plasma samples taken just before the following dose in patients who had had earlier dose(s).

Uncertainty in the knowledge about the unfavourable effects

Despite the existence of a local and regional Safety Officer network to facilitate the reporting of AEs, in developing regions where Voncento is marketed, such as south east Asia and Latin America, there is apparently real underreporting of AE's from these regions which should be addressed by the Applicant. Reporting suspected adverse reactions is addressed in the SmPC (see section 4.8)

There are insufficient data on unfavourable effects in paediatric patients (see SmPC section 4.8). However, although the safety of human coagulation FVIII/VWF complex has not been systematically evaluated in children yet, currently available clinical experience (including the Howman study) and post-marketing information suggest no apparent differences in children compared to adults.

While donor screening and the manufacturing processes used for purification of factor VIII products have improved significantly over the last 20 years, it is still not possible to guarantee total safety of plasma-derived products and this is reflected in the SmPC and PIL.

Benefit-risk balance

Importance of favourable and unfavourable effects

For both indications, the reported degree of efficacy in hemostasis in the treatment of bleeding events and in relation to surgery is adequate and comparable to that reported for other plasma derived VWF and FVIII concentrates in the treatment of severe VWD and hemophilia A.

There were few adverse events reported as being possibly related to Voncento and no reports of development of inhibiting antibodies in the pivotal studies.

Benefit-risk balance

Voncento was effective in inducing hemostasis in bleeding events in patients with severe VWD and in preventing the occurrence of bleeding events in patients with severe hemophilia A. When bleeding events did occur in hemophilia A patients on prophylaxis, Voncento was effective in treating these events. Voncento was also effective in the prevention and treatment of bleeding in relation to surgery. Only mild to moderate adverse events were observed which were not of significance in comparison to the efficacy in the treatment and prevention of bleeding events. The benefit-risk balance is considered positive.

Discussion on the benefit-risk balance

There were concerns about the GCP compliance in the pivotal study submitted by the Applicant to support the efficacy of Voncento in the on-demand treatment of bleeds in VWD as a result of the findings of the EMA GCP inspection. The two sites inspected had also included a significant number of subjects in the hemophilia A study, however the audit commissioned by the applicant was able to address and correct a number of issues and overall the integrity of the data for both studies was found not to be compromised.

Although the efficacy is considered established, the size of the database in the on-demand treatment of bleeds in VWD in the pivotal study CSLCT-BIO-08-54 was small. The Applicant will perform post-marketing studies in both VWD and hemophilia A to provide additional efficacy and safety data. The proposed study in subjects with severe VWD is similar to the pre-authorisation study CSLCT-BIO-08-54. The proposed study in subjects with severe hemophilia A includes 100 adult or adolescent subjects. Post-marketing studies which will be critically evaluated regarding GCP compliance.

At present there are insufficient data on pediatric patients <12 years old for either indication and this is reflected in section 4.2 of the SmPC. Paediatric studies are ongoing with the study reports expected in Q1/Q2 of 2014. Upon completion, the inclusion of paediatric patients < 12 years old in the post-marketing studies CSLCT-BIO-12-83 and CSLCT-BIO-12-78 is foreseen and will be reflected in the next update of the RMP.

The CHMP taking into account that this is in principle a conventional plasma-derived product with documented quality, pharmacokinetics and efficacy/safety and post marketing experience decided that there is no basis for an age restriction in both indications.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Voncento in the treatment of haemorrhage or prevention and treatment of surgical bleeding in patients with Von Willebrand Disease (VWD), when desmopressin (DDAVP) treatment alone is ineffective or contraindicated, and in the prophylaxis and treatment of bleeding in patients with haemophilia A is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal products subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency.

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan (P/107/2011) and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

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