Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Simoctocog Alfa (rhu)

Proprietary Product Name: Nuwiq

Sponsor: Octapharma Australia Pty Ltd

First Round CER 10 December 2013
Second Round CER 14 July 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
AHDCO	Australian Health Minister's Advisory Council
AST	Aspartate aminotransferase
AUC	Area under the curve (from baseline to infinity)
AUC_{norm}	Area under the curve normalised to the dose administered
BDD	B-domain-deleted
BE	Bleeding episode
BLEED	Study population of bleeds treated with simoctocog alfa
BU	Bethesda units
BW	Body weight
CER	Clinical evaluation report
CHMP	Committee for Medicinal Products for Human Use
CHR	Chromogenic
CI	Confidence interval
CL	Clearance
C_{max}	Maximum plasma concentration
$C_{max.norm}$	Maximum plasma concentration normalised to the dose administered
CRF	Case report form
CSR	Clinical Study Report
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ED	Exposure day
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
FDA	Food and Drug Administration
FVIII	Coagulation factor VIII
FVIII:C	FVIII coagulant activity
GCP	Good clinical practice
Hb	Haemoglobin

Abbreviation	Meaning
HBV	Hepatitis B virus
Hct	Haematocrit
HCV	Hepatitis C virus
HLGT	High-level group term
HIV	Human immunodeficiency virus
HJHS	Haemophilia joint health score
IDMC	Independent Data Monitoring Committee
ICH	International Committee for Harmonization
IMP	Investigational medicinal product
ITT	Intention-to-treat
IU	International units
IV	Intravenous
IVR	In vivo recovery
MedDRA	Medical dictionary for regulatory activities
MRT	Mean residence time
N/A	Not available
OS	One-stage
PCR	Polymerase chain reaction
pdFVIII	Plasma-derived coagulation factor VIII
PI	Product Information
PIP	Paediatric investigational plan
PK	Pharmacokinetic
PP	Per-protocol
PROPH	Study population of patients receiving prophylaxis with simoctocog alfa
PT	Preferred term
PTP	Previously treated patient
PUP	Previously untreated patient
rFVIII	Recombinant coagulation factor VIII
SAE	Serious adverse event
SD	Standard deviation
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA queries

Abbreviation	Meaning
SOC	System organ class
SURG	Study population of surgeries treated with simoctocog alfa
$T_{1/2}$	Half-life
TGA	Therapeutic Goods Administration
T_{max}	Time to maximum plasma concentration
V_{ss}	Volume of distribution at steady state
vWD	von Willebrand's disease
vWF	von Willebrand factor

1. Clinical rationale

The following rationale for the submission to register simoctocog alfa was provided in the Clinical Overview and is considered to be acceptable:

Haemophilia A is an inherited sex-linked disorder of blood coagulation in which affected males do not produce functional coagulation FVIII in sufficient quantities to achieve satisfactory haemostasis.[1,2] The incidence of congenital haemophilia A is approximately 1 in 10,000 births. Disease severity is classified according to the level of FVIII activity (% of normal) as mild (>5% to <40%), moderate (1% to 5%) or severe (<1%).[3]

Due to deficiencies in FVIII, patients with haemophilia A are predisposed to recurrent bleeding episodes (BEs). Most BEs occur in joints and muscles. Without adequate treatment these repeated haemarthroses and haematomas lead to long-term sequelae with severe disability. Other less frequent, but more severe bleeding sites are the central nervous system, the urinary or gastrointestinal tract, eyes and the retro-peritoneum. Patients with haemophilia A are at high risk of developing major and life-threatening bleeds after surgical procedures, even after minor procedures such as tooth extraction.

The development of cryoprecipitate and subsequently FVIII concentrates, obtained by fractionation of human plasma, provided replacement FVIII and greatly improved clinical management and life expectancy of patients with haemophilia A. Concerns about virus transmission have largely been ameliorated by the development of FVIII products using recombinant deoxyribonucleic acid (DNA) technology, and full-length and modified rFVIII products produced in hamster cell lines (Chinese hamster ovary [CHO] cells or baby hamster kidney [BHK] cells) are now commercially available for clinical use. As the B-domain is dispensable for FVIII coagulation activity, B-domain deleted BDD FVIII products have been used successfully to treat and prevent BEs in haemophilia A patients. Whilst the introduction of rFVIII products was a major advance in the management of haemophilia A, inhibitors to FVIII have emerged as the major complication of haemophilia A treatment. Simoctocog alfa was developed with the intention to provide a new rFVIII from a human cell line that is potentially less immunogenic.

2. Contents of the clinical dossier

All trade names of comparator products have been replaced by general terms in this document.

2.1. Scope of the clinical dossier

The dossier included a comprehensive data package supporting approval of simoctocog alfa for the treatment of severe haemophilia A in previously treated adults and children aged 2 years and above. There were no clinical data in the submission supporting approval of simoctocog alfa for the treatment of previously treated children aged less than 2 years of age (including newborns). There were no clinical data in the submission supporting approval of simoctocog alfa for the treatment of previously untreated patients with severe haemophilia A.

The relevant clinical information provided in the dossier is summarised below:

- Five clinical studies each including pharmacokinetic (PK), efficacy and safety data (GENA-01, -03, -08, -09, -04); one of the five studies included data in children aged 2 to 12 years (GENA-03).
- Literature references
- Clinical Overview; Clinical Summary containing Summary of Biopharmaceutic Studies and Associated Analytical Methods, Summary of Clinical Pharmacology Studies, Summary of

Clinical Efficacy, Summary of Clinical Safety, Literature References, Synopsis of Individual Studies, and Appendices.

2.2. Paediatric data

The submission included one clinical study (GENA-03) providing PK, efficacy and safety data in 59 previously treated male children between aged 2 to 12 years (29 aged 2-5 years; 30 aged 6-12 years). The submission included a statement concerning the *Paediatric Development Programme*. The statement indicated that the sponsor has an agreed European Paediatric Investigation Plan (PIP) dated 22 February 2013.

2.3. Good clinical practice

The sponsor stated that all clinical studies with simoctocog alfa were conducted in accordance with the regulations of the International Committee for Harmonization (ICH) on Good Clinical Practice (GCP).

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

FVIII is a normal constituent of human plasma and is predominantly produced in the liver, but also by other tissues such as the kidney, lymph nodes and spleen. FVIII circulates in the plasma non-covalently bound to von Willebrand factor (VWF). Each FVIII molecule can bind to a VWF monomer, but the actual ratio is 1:50. The sponsor states that it is commonly acknowledged that appropriate PK data (incremental recovery, half-life [T1/2], area under the concentration curve [AUC], and clearance [CL]) are the most important (surrogate) endpoints for efficacy of a new FVIII product.[4]

The primary pharmacokinetic (PK) data were derived from 3 multinational, multicentre studies, including GENA-01 and GENA-08 in adults and GENA-03 in children aged 2-12 years. The supportive PK data were provided by 2 studies in adults, GENA-09 (a single-centre study undertaken in Russia that enrolled adult patients with severely affected joints and high historical bleeding rates) and GENA-04 (an extension study to GENA-09). The determination of PK parameters was the primary objective of both GENA-01 and GENA-09. In addition to PK data, all 5 clinical studies included efficacy and safety data. Consequently, data from these 5 studies have been evaluated in the *Pharmacokinetics*, *Efficacy*, and *Safety Sections* of this CER.

Three studies (GENA-01, GENA-03 and GENA-09) included full analyses of all relevant PK parameters. Two of these studies (GENA-01 and GENA-09) used a randomised cross-over design to compare the PK parameters of simoctocog alfa with those of a full-length rFVIII concentrate. In addition, GENA-01 included a formal bioequivalence analysis comparing simoctocog alfa with a full length rFVIII concentrate [information redacted]. In addition to initial bioequivalence testing and PK analysis, the PKs of simoctocog alfa were also assessed after 6 months treatment for on-demand bleeding in GENA-01 and for prophylaxis and on-demand treatment for breakthrough bleeding in GENA-09. In accordance with the EMA *Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products (EMEA/CHMP/BPWP/144533/2009)*, PK parameters in the paediatric study (GENA-03) were determined only at the start of the study, first for the previously used FVIII concentrate (pdFVIII or rFVIII) and subsequently for simoctocog alfa. In the remaining two studies, GENA-04 and GENA-08, only *in vivo* recovery (IVR) data were collected. An overview of the studies providing PK assessment of simoctocog alfa is provided below in Table 1.

Table 1: Overview of studies providing PK/IVR data for simoctocog alfa.

	GENA-01 Pivotal	GENA-08 Pivotal	GENA-03 Pivotal	GENA-09 Supportive	GENA-04 Supportive
Patients*	22 PTPs 12–65 years	32 PTPs 18–75 years	59 PTPs (26 for PK) 2–12 years	22 PTPs 18–62 years	18 PTPs who completed GENA-09
PK assessment (including IVR)	Baseline (comparator: a full-length rFVIII BHK) 6 months (only simoctocog alfa)	–	Baseline† (comparator: previous FVIII concentrate)	Baseline (comparator: a full-length rFVIII BHK) 6 months (only simoctocog alfa)	–
IVR assessment only	3 months	Baseline 3 months 6 months	Baseline# 3 months* 6 months*	3 months	3 months and then 3-monthly until study end
Immunogenicity	Yes	Yes	Yes	Yes	Yes
Efficacy	Yes	Yes	Yes	Yes	Yes

* All patients; # Patients not participating in the PK phase of the study.
AUC = area under the curve; AUC_{norm} = area under the curve normalised to the dose administered; CL = clearance; C_{max} = maximum plasma concentration; $C_{max.norm}$ = maximum plasma concentration normalised to the dose administered; IVR = in vivo recovery; MRT = mean residence time; PK = pharmacokinetic; PTP = previously treated patient; $T_{1/2}$ = half-life; T_{max} = time to maximum plasma concentration; V_{ss} = volume of distribution at steady state.

3.2. Summary of pharmacokinetics

3.2.1. Physicochemical characteristics of the active substances

The following information has been summarised from the sponsor's Clinical Overview:

Simoctocog alfa is a B-domain-deleted (BDD) fully-sulphated glycoprotein with complex-, hybrid- and high mannose-type glycosylation present at the same sites as in native human pdFVIII. The types of *N*-glycans at the respective *N*-glycosylation sites for simoctocog alfa are identical to those found in pdFVIII. The oligosaccharide structures are highly similar with mainly small, quantitative differences of certain glycosylation features. In functional studies, simoctocog alfa was shown to have high specific FVIII activity and characteristics similar to full-length rFVIII products and exhibited physiological thrombin generation, a normal rate of inactivation by activated protein C and high binding capacity with VWF. Expression in a human cell line avoids the potential for incorporation of non-human glycan epitopes, such as the carbohydrate epitopes α-Gal and Neu5Gc, which have been shown to be immunogenic. The human-like glycosylation pattern with the absence of immunogenic epitopes seen in rFVIII products produced from hamster cells may provide a less immunogenic product.

3.3. Assessment of FVIII:C plasma levels and determination of PK parameters

In all studies, PK assessments for simoctocog alfa were undertaken following a dose of 50 IU FVIII/kg according to the labelled potency, but the PK parameters were calculated using actual potency determined a central laboratory located in the USA. FVIII coagulant activity (FVIII:C) in plasma was determined both by the chromogenic (CHR) and one-stage (OS) assays by the same central laboratory for all studies. It was stated that the central laboratory established acceptable intra- and inter-assay precision for both assays.

The PK parameters were calculated using standard non-compartmental analysis (NCA) with standard PK software packages. The provided PK parameters were consistent with those outlined in the relevant TGA adopted EU guidance document. The tabulated summary is from GENA-03, but is applicable to all studies with PK data included in the submission.

3.4. Primary pharmacokinetics studies in patients with haemophilia A

3.4.1. GENA-01 - previously treated adolescent and adults (aged 12 to 65 years)

Title

Clinical Study To Investigate The Pharmacokinetics, Efficacy, Safety And Immunogenicity Of Simoctocog alfa, A Newly Developed Human Cell-Line Derived Recombinant FVIII Concentrate In Previously Treated Patients With Severe Haemophilia A.

Location

The study was undertaken in Bulgaria (1 site), Germany (1 site) and the USA (7 sites), between 27 May 2010 and 18 September 2012. The CSR was dated 15 February 2013. The study was conducted in accordance with standard ethical requirements.

Objectives

The primary objective of this study was to determine the pharmacokinetics (PKs) of simoctocog alfa based on FVIII coagulant activity (FVIII:C) and to compare them with the PKs of a full-length rFVIII BHKconcentrate in previously treated patients (PTPs) suffering from severe haemophilia A. The comparator was chosen by the sponsor in consultation with the FDA. The sponsor states that the full-length rFVIII BHK product was purchased in the USA for the USA study centres, and in Germany for the German and Bulgarian study centres. The study also included secondary objectives assessing the incremental recovery of FVIII:C for simoctocog alfa, the immunogenic potential of simoctocog alfa, and the efficacy and safety of simoctocog alfa for the treatment of bleeding episodes (BEs) and for surgical prophylaxis.

Design

GENA-01 was designed as a prospective, randomised, actively-controlled, open-label, cross-

over, multicentre Phase II study in previously treated patients (PTPs) with severe haemophilia A (FVIII:C ≤ 1%). The study included two parts. In Part I (PK phase), the PK properties of simoctocog alfa and a full-length rFVIII were studied. In Part II, subjects who completed Part I were treated for at least 6 months or until 50 exposure days (EDs) were reached, whichever came last. During Part II, the effects of on-demand treatment with simoctocog alfa on BEs was documented, and the PKs of simoctocog alfa were assessed at 6 months in those subjects with PK data from the start of the study (that is, from Part I).

In Part 1 of the study, the visit for PK Cycle 1 was scheduled no later than 4 weeks after the screening visit, but may have been postponed in patients with BEs. Patients were randomised to receive 50 international units (IU) FVIII/kg BW (labelled potency) of either simoctocog alfa or a full-length rFVIII in Cycle 1 and the alternative product in Cycle 2, after a wash-out period of at least 96 hours. The time period between PK Cycle1 and start of PK Cycle 2 was to be no longer than 4 weeks, but may have been postponed in patients with BEs. The FVIII products were administered by iv bolus injection at a maximum speed of 4 mL/minute.

Actual body weight was to be documented before administration of the FVIII products. Vital signs were to be analysed before, and at 1, 24 and 48 hours after FVIII administration, and safety laboratory assessments were to be undertaken before, and at 24 hours (excluding urinalysis) and 48 hours after FVIII administration. Blood samples for the determination of FVIII:C levels were to be taken before and at 0.25, 0.5, 0.75, 1, 3, 6, 9, 12, 24, 30 and 48 hours after the end of the FVIII injection. Actual time-points were to be documented.

Pharmacokinetic assessments and statistical methods

The primary PK endpoint was the AUC_{inf} of simoctocog alfa normalised to the dose administered (AUC_{norm}) compared with a full-length rFVIII calculated for FVIII:C. In Part I, descriptive statistics were provided for AUC_{norm} per treatment as well as for the estimated Ratio AUC_{norm} with 90% confidence intervals (CIs).

As an additional analysis of the primary efficacy endpoint, a formal statistical test was performed to determine whether the Ratio AUC_{norm} for the two FVIII products was between 80% and 125% (that is, the standard bioequivalence interval). The null hypothesis (H0) was Ratio $AUC_{norm} < 0.8$ or Ratio $AUC_{norm} > 1.25$, and the alternative hypothesis (H1) was $0.8 \leq$ Ratio $AUC_{norm} \leq 1.25$. The 90% CI of the Ratio AUC_{norm} was calculated using standard statistical methods for the determination of bioequivalence, and the two products were deemed to be bioequivalent if the 90% CI was completely enclosed within the range 80% to 125% (that is, null hypothesis was rejected).

The sample size of 20 enrolled patients in Part 1 (PK phase) of the study was chosen by the sponsor in consultation with the FDA. The power to have a significant test under the alternative hypotheses (at least for RatioAUC_{norm}= 0.8, 1 and 1.25) was calculated retrospectively with the estimated treatment effect and the empirical standard deviations found in the data. Based on these data, the retrospective power of the test to show that the geometric mean ratio of AUC_{norm} for simoctocog alfa over full-length rFVIII BHKwas within the range 0.8 to 1.25 was 81% for the CHR assay and 77% for the OS assay.

The primary tests were in the PK-PP population for the CHR assay, and were repeated as a secondary analysis for the intention-to-treat (ITT) population and the OS assay. The PK-PP population consisted of all randomised subjects who completed Part 1 (PK phase) of the study and had received both treatments without significantly violating the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the PK results.

The secondary PK endpoints were calculated for FVIII:C using both the CHR and the OS assays and the actual potency of the drugs. The secondary PK endpoints were $T_{1/2}$, maximum plasma concentration (C_{max}), maximum plasma concentration normalised to dose ($C_{max.norm}$), time at maximum concentration (T_{max}), mean residence time (MRT), volume of distribution at steady state (V_{ss}), and clearance (CL). The same statistical methods were used to analyse the primary

and secondary PK endpoints.

In vivo incremental recovery (IVR) of FVIII:C (CHR and OS assays) was assessed during the PK Phase in Cycles 1 and 2 for simoctocog alfa and a full-length rFVIII BHK, and at 3 and 6 months after the start of the open phase for simoctocog alfa. Incremental recovery was calculated from the FVIII:C level before infusion and the peak FVIII:C level after infusion obtained in the 0.25, 0.5, 0.75, or 1 hour post-infusion samples. For the calculation of recovery, the actual potency of simoctocog alfa was used, and the results were summarised using descriptive statistics. The following formula was used to calculate recovery:

Recovery = (C_{max} - plasma concentration at baseline) * BW/dose; and results were reported as (IU/dL)/(IU/kg) (that is, % per IU/kg).

Chromogenic (CHR) and one-stage (OS) assays

The PK characteristics of simoctocog alfa and a full-length rFVIII BHK were compared using both CHR and the OS assays. FVIII:C levels were calculated using validated methods for OS and CHR assays in a central laboratory, which also assigned the actual drug potency by means of the same assays. In addition to measuring FVIII:C levels and potencies of the FVIII products using CHR and OS assays the central laboratory also measured FVIII inhibitor levels and anti-recombinant FVIII (rFVIII) antibody levels. Local laboratories did all other tests. In case of surgery, FVIII:C could also have been measured locally.

Demographics of the PK study population

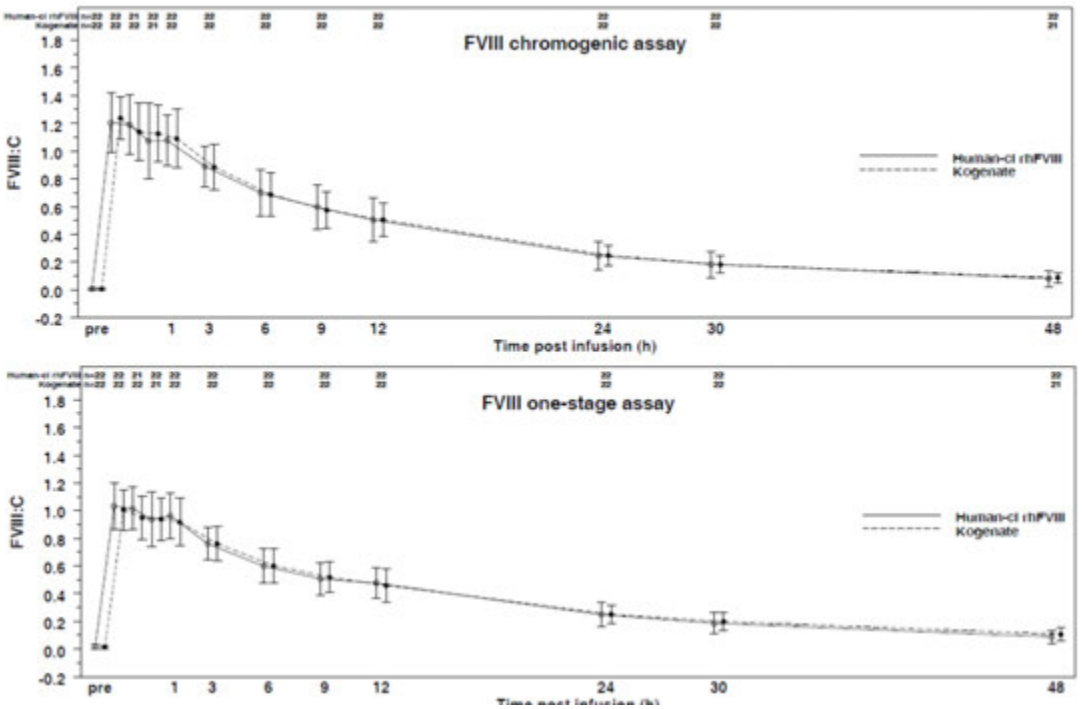
A total of 22 patients were enrolled and included in the safety (SAF) and the ITT populations. All 22 enrolled patients were included into the PK-PP primary analysis population (Part I) and 21 of the 22 enrolled patients were included in the PK-6m-PP population (that is, all enrolled subjects who completed the PK assessment 6 months after the start of the study without significantly violating the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the PK results). One (1) enrolled patient was excluded from the PK-6m-PP population because of an implausible concentration time profile after the 6-month PK infusion.

The 22 patients were between 12 and 65 years of age, with a median age of 39.6 years. The total Haemophilia Joint Health Score (HJHS) at baseline ranged from 0 to 84, with a mean score of 38.4. The majority (n=18, 81.8%) of patients were white. A family history of haemophilia was documented in 14 (63.6%) patients and 2 (9.1%) patients had a family history of inhibitors. FVIII inhibitor levels were less than 0.6 BU in 16 patients at screening, as measured by both the Bethesda and the Nijmegen assays, and in 6 (27.3%) patients FVIII inhibitors at screening could not be determined due to the remaining pre-study FVIII plasma levels being too high for the test to give reliable results. However, all 6 patients were negative for FVIII inhibitors pre-infusion at PK Cycle 1.

Pharmacokinetic results for simoctocog alfa and full-length rFVIII BHK FS - Part 1 (cycle 1)

The actual doses administered for the PK assessment (Cycle 1) were 58.3±3.7 IU/kg for simoctocog alfa and 55.8±2.9 IU/kg for full-length rFVIII BHK FS as determined by the CHR assay, and 48.6±3.3 IU/kg and 64.3±5.6 IU/kg, respectively, for the OS assay. The mean FVIII:C concentrations over time profiles through to 48 hours, after standardising for actual doses and according to both assays, are shown below in Figure 1.

Figure 1: GENA-01 - FVIII:C levels (IU/mL, mean±SD) standardised to 50 IU/kg for both assays; PK-PP population, n=22.



The mean values for the AUC_{norm} (primary PK efficacy endpoint) for the two FVIII products,, as determined by the CHR and OS assays, are summarised below in Table 2. The mean values for the secondary PK parameters during Part I of the study are summarised below in Table 3. The geometric mean ratios and 90% CIs of the secondary PK parameters were provided.

Table 2: GENA-01 - Comparative ANOVA results for AUCnorm (h•IU/mL/[IU/kg]); PK-PP population, n=22.

Assay	Treatment	Mean	SD	Ratio of gmeans	90% CI
CHR	Simoctocog alfa	0.39	0.14	0.98	0.8741, 1.107
	full-length rFVIII BHK	0.38	0.09		
OS	Simoctocog alfa	0.37	0.11	0.97	0.859, 1.088
	full-length rFVIII BHK	0.38	0.11		

Table 3: GENA-01 - Secondary PK parameters for the two products measured by the CHR and OS assays during Part 1 (PK phase); PK-PP population, n=22.

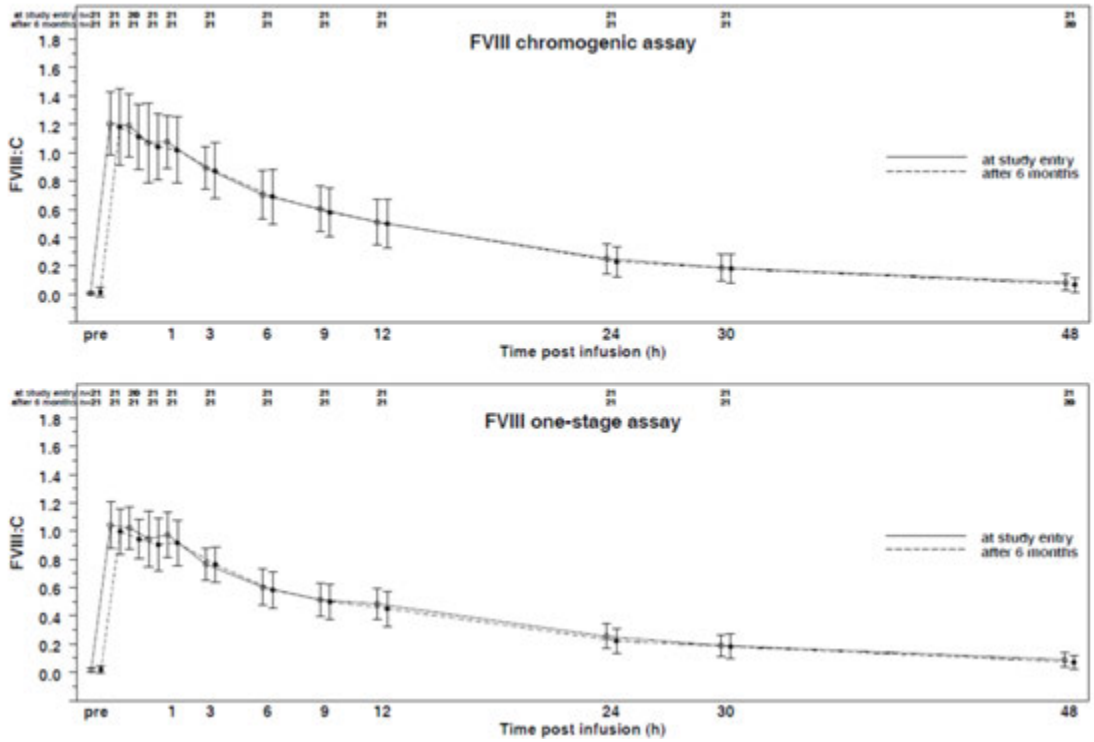
Parameter	Simoctocog alfa [CHR]	full-length rFVIII BHK [CHR]	Simoctocog alfa [OS]	full-length rFVIII BHK [OS]
AUC (h·IU/mL)	22.5 ± 7.8	21.3 ± 4.7	18.0 ± 5.6	24.2 ± 6.0
Cmax (IU/mL)	1.46 ± 0.22	1.39 ± 0.20	1.05 ± 0.15	1.31 ± 0.18
Cmax.norm (IU/mL per IU/kg)	0.025 ± 0.004	0.025 ± 0.003	0.022 ± 0.003	0.021 ± 0.003
IVR (% per IU/kg)	2.50 ± 0.37	2.49 ± 0.32	2.14 ± 0.27	2.03 ± 0.28
Tmax (h)	0.35 ± 0.23	0.34 ± 0.20	0.43 ± 0.28	0.41 ± 0.27
T1/2 (h)	14.7 ± 10.0	16.1 ± 5.9	17.1 ± 11.2	18.8 ± 5.9
MRT (h)	19.5 ± 12.0	20.0 ± 5.6	22.5 ± 14.2	24.2 ± 6.8
CL (mL/h/kg)	2.94 ± 1.18	2.75 ± 0.64	2.96 ± 0.97	2.82 ± 0.72
Vss (mL/kg)	49.6 ± 17.3	53.3 ± 13.6	59.8 ± 19.8	64.8 ± 12.8

Comment: FVIII:C levels over time were virtually identical for simoctocog alfa and full-length rFVIII BHK, as determined by both the CHR and OS assays. However, FVIII:C levels determined by the OS assay were generally lower at all time points compared with corresponding levels determined by the CHR assay. In Part 1 (PK), when measured by the OS assay the mean dosage of full-length rFVIII BHKwas approximately 16 IU/kg higher than the mean dosage of simoctocog alfa, but when measured by the CHR assay it was approximately 2 IU/kg lower. The two products were bioequivalent based on the geometric mean ratios of the AUC_{norm} determined by both the CHR and the OS assays. The results for the secondary PK endpoints were similar for the two products when determined by both the CHR and the OS assays. There were some differences in the results for the secondary PK parameters of simoctocog alfa when measured by the CHR and OS assays. However, these differences are unlikely to be clinically significant.

Pharmacokinetic parameters for simoctocog alfa - 6 months after initiation of treatment

The PK parameters following simoctocog alfa administration were also assessed 6 months after the study start in 21 patients (PK-6m-PP). For this PK assessment, the mean±SD actual simoctocog alfa dose was 58.5±4.8 IU/kg as determined by the CHR assay, and 49.8±4.0 IU/kg as determined by the OS assay. FVIII:C levels (mean±SD) versus time profiles through to 48 hours and standardised to 50 IU/kg for simoctocog alfa were similar at study entry and month 6, as measured by both CHR and OS assays (see Figure 2, below).

Figure 2: GENA-01 - FVIII:C levels (IU/mL, mean±SD) at study entry and at month 6, standardised to 50 IU/kg for both the CHR and the OS assays; PK-6m-PK population, n=21.



The PK parameters for simoctocog alfa at 6 months after the study start in 21 patients (PK-6m-PP) are summarised below in Table 4, as are geometric mean ratios (90% CI) for month 6 relative to Cycle 1 (study start) in the 21 patients in the PP-PK with data at both time-points.

Table 4: GENA-01 - PK parameters for simoctocog alfa measured by both assays at month 6 (PK-6m-PP; n=21), and geometric mean (Gmean [90% CI]) ratios at 6 months relative to study start (PK-PP; n=21).

Parameter	CHR - 6 months	OS - 6 months	Gmean Ratio (CHR)	Gmean Ratio (OS)
AUC (h·IU/mL)	21.24 ± 8.81	16.86 ± 6.12	-	-
AUCnorm (h·IU/mL/[IU/kg])	0.36 ± 0.13	0.34 ± 0.11	0.90 [0.808, 1.009]	0.88 [0.795, 0.970]
Cmax (IU/mL)	1.42 ± 0.39	1.04 ± 0.20	-	-
Cmax.norm (IU/mL/[IU/kg])	0.024 ± 0.005	0.021 ± 0.003	0.94 [0.868, 1.027]	0.95 [0.880, 1.019]
IVR (% per IU/kg)	2.37 ± 0.49	2.05 ± 0.31	0.94 [0.867, 1.023]	0.94 [0.879, 1.015]
Tmax (h)	0.32 ±	0.57 ±	-	-

Parameter	CHR - 6 months	OS - 6 months	Gmean Ratio (CHR)	Gmean Ratio (OS)
	0.18	0.35		
T1/2 (h)	12.7 ± 4.1	14.1 ± 4.7	0.92 [0.790, 1.078]	0.87 [0.746, 1.023]
MRT (h)	16.8 ± 5.9	18.8 ± 6.8	0.91 [0.794, 1.037]	0.87 [0.756, 1.001]
CL (mL/h/kg)	3.33 ± 1.80	3.39 ± 1.42	1.11 [0.991, 1.237]	1.14 [1.031, 1.259]
Vss (mL/kg)	48.9 ± 10.7	56.9 ± 9.1	1.01 [0.906, 1.115]	0.99 [0.888, 1.106]

Comment: When measured by the CHR assay, most PK parameters for simoctocog alfa were similar at 6 months and at study start, with the exception of $T_{1/2}$ and MRT, which were both shorter at 6 months than at study start. When measured by the OS assay, the mean AUC_{norm} was lower, and both the mean $T_{1/2}$ and MRT were shorter at month 6 than at study start, while the mean CL was higher at month 6 than at study start. The differences between the $T_{1/2}$ and MRT at 6 months and study start in the 21 patients in the PK-PP population may have been due to one patient from the Bulgarian centre having an unusually long $T_{1/2}$ at study entry (55.6 h by CHR assay and 64.8 h by OS assay). In addition, 3 patients from the Bulgarian centre had unusually low AUC_{norm} ratios (6 months vs initial PK) for simoctocog alfa. In view of the anomalous results from the Bulgarian centre the sponsor undertook an exploratory analyses of the PK parameters for simoctocog alfa at 6 months (CHR and OS assays) excluding the 6 patients from this centre. In these exploratory analyses, the PK parameters for simoctocog alfa at 6 months and at study start were similar. The PK results at 6 months in the both the total 21 PK-6M-PP and the 15 PK-6m-PP (excluding the Bulgarian centre) were provided.

In vivo recovery (IVR) results over time

All 22 patients in the ITT population underwent IVR analysis at study entry (Part I) and at 3 months and 6 months after start of on-demand treatment. For IVR analysis, patients received 50 IU/kg of simoctocog alfa (labelled potency) after a wash-out period of at least 96 hours for the first and 6 month visits and 72 hours for the 3 month visit. The mean doses administered for the IVR analysis determined by the CHR assay were 58.3±3.7 IU/kg, 59.0±5.2 IU/kg and 58.7±4.8 IU/kg at study start, 3 months and 6 months, respectively. Corresponding doses determined by the OS assay were 48.6±3.3 IU/kg, 50.3±4.2 IU/kg and 50.0±4.0 IU/kg. The results are summarised below in Table 5.

Table 5: GENA - 01 - In vivo recovery (IVR; % per IU/kg) for simoctocog alfa at study entry, and 3 and 6 months after the start of on-demand treatment; ITT population n=22.

Time point	Assay	Mean	SD	Median	Range
Study entry (Part 1)	CHR assay	2.50	0.37	2.46	1.668 - 3.150
	OS assay	2.14	0.27	2.13	1.713 - 2.787
3 months	CHR assay	2.44	0.56	2.49	1.607 - 3.629
	OS assay	2.06	0.39	2.05	1.482 - 3.106
6 months	CHR assay	2.34	0.50	2.41	1.338 - 3.785
	OS assay	2.01	0.33	1.98	1.375 - 2.680

Comment: The mean IVR values were within the range of 2.0% to 2.5% per IU/kg, which is line with expected values. All except 3 individual values for IVR were higher than 1.5% per IU/kg, and these 3 individual values were lower than 1.5% when measured by one or other of the two assays but not by both. Overall, IVR values obtained with the OS assay were generally lower than those obtained with the CHR assay. Mean recoveries at 3 months and at 6 months were slightly lower than those at study entry. The geometric mean ratio for IVR for simoctocog alfa at 6 months relative to study start in the ITT population was 0.93 (90% CI: 0.850, 1.007) as determined by the CHR assay, and 0.94 (90% CI: 0.870, 1.010) as determined by the OS assay.

Conclusions relating to the PK data from study GENA-01

In this study the PKs of simoctocog alfa were assessed in 22 patients. The study planned to recruit patients at least 12 years of age, however, only 2 patients were aged less than 18 years. The median age of patients in the study was 39.6 years and 81.8% were "white".

.The FVIII:C levels (IU/mL) versus time profiles to 48 hours post-administration were similar for simoctocog alfa and full-length rFVIII BHK, as determined by both the CHR and OS assays. The study demonstrated that simoctocog alfa was bioequivalent to full-length rFVIII BHK, based on the AUCnorm (primary PK endpoint) calculated using data from both the CHR an OS assays. The ratio of geometric means (90% CI]) for simoctocog alfa relative to full-length rFVIII BHKfor the AUC_{norm} was 0.98 (90% CI: 0.874, 1.107) as determined by the CHR assay, and 0.97 (90% CI: 0.859, 1.088) as determined by the OS assay.

In the PK-PP population, the results for the secondary PKs parameters for simoctocog alfa were similar to the corresponding results for full-length rFVIII BHK as determined by both the CHR and OS assays. The 90% CIs of the ratios of simoctocog alfa relative to full-length rFVIII BHK were enclosed within the BE limits of 0.80 to 1.25 for the secondary PK endpoints of $C_{max.norm}$, IVR, CL and V_{ss} as determined by the CHR and OS assays. However, the $T_{1/2}$ and MRT values for full-length rFVIII BHKwere longer than for simoctocog alfa as determined by both the CHR and OS assays, and the 90% CIs of the ratios for the two parameters were outside the BE limits of 0.80 to 1.25 (lower limits being < 0.80). According to the CHR assay, the mean $T_{1/2}$ for

simoctocog alfa was 14.73 hours compared with 16.14 hours for full-length rFVIII BHK, and the results for MRT were 19.45 and 20.00 hours, respectively. According to the OS assay, the mean $T_{1/2}$ for simoctocog alfa was 17.05 hours compared with 18.75 hours for full-length rFVIII BHK, and the results for MRT were 22.47 and 24.18 hours, respectively.

The mean IVR values were consistent over time and were within the range 2.0% to 2.5% per IU/kg at study start, 3 months, and 6 months, as determined by both the CHR and the OS assays. However, the mean IVR values at each time-point were about 14% to 16% lower as determined by the OS assay compared with the CHR assay. The sponsor states that theunderestimation of FVIII activity by OS assay has been identified for other B-domain deleted products.[5,6] In Morfini et al (2003),[5] it was reported that plasma levels of FVIII were underestimated by 40% to 50% when measured by the OS assay compared with the CHR assay after infusion of B-domain deleted recombinant FVIII. In Lippi et al (2009),[6] it was reported that plasma levels of FVIII were underestimated by 20% to 50% when measured by the OS assay compared with the CHR after infusion of B-domain deleted recombinant FVIII in patients with severe haemophilia A.

3.4.2. GENA-03 - previously treated children aged 2 to 12 years

a. Title

Prospective Clinical Study in Children with Severe Haemophilia A to Investigate Clinical Efficacy, Immunogenicity, Pharmacokinetics, and Safety of Simoctocog alfa.

b. Location and study dates

The study was conducted at 15 investigational centres in the UK, Czech Republic, Poland, Russia, Turkey, France and Romania. The Co-ordinating Investigator was located at the Great Ormond Street Hospital for Children, NHS Trust Haemophilia Centre, London, UK. The study was conducted from 17 December 2010 to 6 November 2012, and the CSR was dated 13 February2013. The study was conducted in accordance with standard ethical requirements.

c. Objectives

The *primary objective* of the study was to assess the clinical efficacy of simoctocog alfa in terms of prevention and treatment of breakthrough BEs in patients receiving prophylaxis.

The *secondary objectives* of the study were to: determine the pharmacokinetics (PK) of simoctocog alfa in up to 13 patients (12 evaluable) in each age group (2 to 5 and 6 to 12 years); to compare the PK results for simoctocog alfa with the PK results of previously used FVIII concentrate; to determine the incremental recovery of simoctocog alfa over time; to investigate the immunogenic potential of simoctocog alfa by assessing the inhibitor titre; to assess efficacy of simoctocog alfa in surgeries; and to assess safety of simoctocog alfa in terms of adverse event (AE) monitoring.

d. Design

GENA-03 was designed as a prospective, non-controlled, open-label, multicentre, Phase III study in 59 previously treated children with haemophilia A aged 2 to 12 years. All children in the study population had previously experienced at least 50 exposure days (EDs) to FVIII concentrates.

The study included two phases. In Phase I, the PKs of simoctocog alfa and the previously used licensed FVIII concentrate (recombinant or plasma derived) were investigated in a subset of 27 patients in a non-randomised, cross-over design. In Phase II, patients who had completed Phase I plus an additional 32 enrolled patients were treated with prophylactic and on-demand simoctocog alfa and followed up for a period of at least 6 months and at least 50 EDs.

In Part I of the study, the PK characteristics of the previously used FVIII concentrate (PK Cycle 1) and simoctocog alfa (PK Cycle 2) were analysed in 26 patients in the PK-PP population (13 patients aged 2–5 years; 13 patients aged 6–12 years). PK Cycle 1 was to take place no later than

4 weeks after the screening visit. The previous FVIII concentrate (PK Cycle 1) was to be administered after a 72 hour wash-out, and the wash-out period between PK Cycle 1 and PK Cycle 2 was to be at least 72 hours. Both the previous FVIII product and simoctocog alfa were administered at a dose of 50 IU FVIII/kg (labelled potency). When possible, both PK cycles were performed one after the other (that is, within 1 week, including wash-out period). Where this was not possible the two PK cycles were to be performed within a maximum of 4 weeks.

Prior to administration of the previous FVIII concentrate (PK Cycle 1), actual BW was documented and baseline assessments were undertaken for FVIII:C level, FVIII inhibitors, anti-rhFVIII antibodies, safety laboratory tests and vital signs. In addition, at 48±2 hours after the end of the infusion in both PK Cycles 1 and 2 assessments were undertaken for FVIII:C level, FVIII inhibitors, safety laboratory tests and vital signs. AE monitoring was undertaken throughout the whole period in both PK Cycle 1 and 2.

e. Pharmacokinetic assessments and statistical methods

In Phase I of the study, PK analysis was undertaken with the previously used FVIII concentrate, and with simoctocog alfa. The following PK parameters were calculated for both products by NCA based on both the CHR and OS assays and the actual potency of both FVIII concentrates: AUC and AUC normalised by the dose (AUC_{norm}), $T_{1/2}$, C_{max}, T_{max}, MRT, V_{ss}, and CL. The PK analyses were based on FVIII:C plasma levels measured before and 30 minutes, 2, 5, 10, 24, and 48 hours after the end of injection. Descriptive parameters were provided for all PK parameters. Individual comparisons of the PK ratios of simoctocog alfa with previously used FVIII concentrate were calculated. All calculations (except T_{max}) were based on actual sampling times rather than on nominal time points. FVIII:C values below the limit of quantification were set to zero for PK calculations.

The IVR was calculated at study entry for all patients and after 3 and 6 months of treatment from the FVIII:C plasma level before and peak levels obtained 30 minutes and 2 hours post-infusion. For the calculation of recovery, the actual potency of simoctocog alfa and the previously used FVIII concentrate was used. The IVR was calculated using the same formula as that employed in GENA-01.

No formal sample size calculation was performed for this study, but the sample size was chosen to satisfy CHMP criteria (EMEA/CHMP/BPWP/144533/2009; London, 23 July 2009).

The primary analysis population for the PK data (Phase I) was the PK per protocol (PK-PP) analysis population. The PK-PP analysis population included all patients who completed the PK-phase of the trial and received both FVIII treatments without significantly violating the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the PK results.

f. Chromogenic (CHR) and one-stage (OS) assays

FVIII:C levels for calculation of IVR and PK were performed using validated methods for OS and CHR assays in the central laboratory, which also assigned the actual drug potency by means of the same assays. In addition, FVIII inhibitory and non-inhibitory antibodies against simoctocog alfa were also measured by validated methods in the central laboratory.

g. Demographics of the PK study population

PK analysis was undertaken in 27 patients (45.7% of the total population) using their previous FVIII concentrate and simoctocog alfa. However, the PK-PP analysis population included 26 patients as one of the 27 studied patients was subsequently excluded due to a diagnosis of von Willebrand disease (VWD). Of the 26 patients in the PK-PP analysis population, 13 were aged between 2 and 5 years and 13 were aged between 6 and 12 years.

Comment: No separate tabulated summary of the demographics of the 26 patients in the PK-PP population could be identified in the submission. The sponsor will be requested to

provide this information in its s31 response to the first round clinical evaluation. *See Section 11.1.1.*

h. PK results - actual doses

Patients received their previously used FVIII concentrate after at least a 72-hour wash-out at a dose of 50 IU/kg BW (labelled potency) in PK Cycle 1 followed by at least a 72-hour washout period, and simoctocog alfa at the dose of 50 IU/kg BW (labelled potency) in PK Cycle 2. Some actual potencies for the previously used FVIII products were not available and in these cases the certificates of analysis were obtained and used for the PK evaluation. Furthermore, not all previous FVIII concentrates were analysed and in these cases actual potency was calculated from mean potency over identical product lots weighted by the administered amount per lot. The actual doses administered according to potencies measured with the CHR and OS assays are summarised below in Table 6.

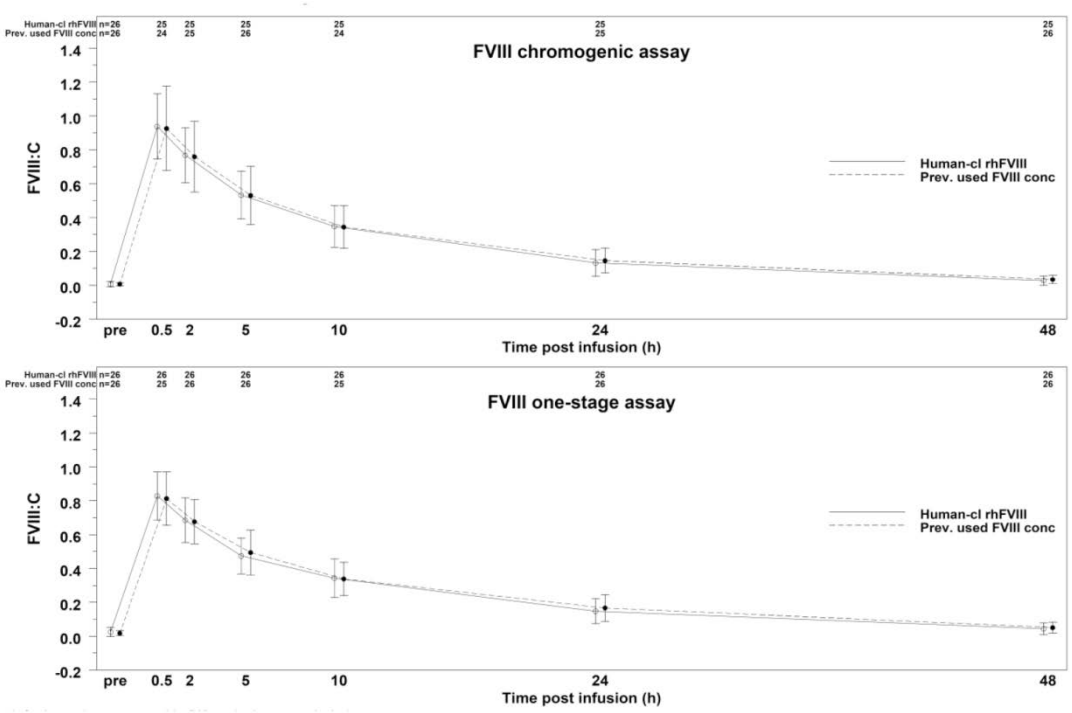
Table 6: GENA-03 - Actual dose (IU/kg) administered for PK analysis; PK-PP population (n=26).

Assay	Cycle	FVIII product	Mean	SD	Median	Range
CHR assay	Cycle 1	Previous FVIII	43.8	4.8	42.8	35.7–53.8
	Cycle 2	Simoctocog alfa	53.1	1.5	53.8	48.2–56.8
OS assay	Cycle 1	Previous FVIII	52.2	4.2	51.3	46.7–64.7
	Cycle 2	Simoctocog alfa	45.4	1.1	45.2	42.4–49.1

i. PK results - FVIII plasma concentrations

FVIII:C levels (mean±SD) versus time profiles through to 48 hours and dose standardised to 50 IU/kg, as determined by both CHR and OS assays, for the total paediatric population (2 to 12 years of age) are provided below in Figure 3 and the corresponding results for the 2-5 and 6-12 age sub-groups were also provided.

Figure 3: GENA-03 - Mean± SD FVIII levels (IU/mL) during PK assessment (Phase I), standardised to 50 IU/kg; PK-PP population, n=26



Comment: There were no marked differences between FVIII:C peak levels of rates of decrease for previously used FVIII concentrates and simoctocog alfa in the total paediatric population, or the two sub-groups based on age.

j. PK results (Cycles 1 and 2) for the total paediatric population aged 2 to 12 years

The PK parameters (mean±SD) for previous FVIII concentrates (PK Cycle 1) and simoctocog alfa (PK Cycle 2), as determined by the CHR and OS assays, are shown below in Table 7 for the total paediatric population aged 2-12 years.

Table 7: GENA-03 - PK parameters (mean±SD) for simoctocog alfa and previous FVIII concentrates measured by the CHR and OS assays; PK-PP population for the 2 - 12 years age group, n=26 (OS assay) and n=25 (CHR assay).

Parameter	Simoctocog alfa [CHR]	Previous FVIII [CHR]	Simoctocog alfa [OS]	Previous FVIII [OS]
AUC (h·IU/mL)	12.39 ± 4.47	10.77 ± 4.66	10.92 ± 3.80	13.22 ± 5.03
AUCnorm (h·IU/mL [IU/kg])	0.23 ± 0.08	0.24 ± 0.09	0.24 ± 0.08	0.25 ± 0.09
Cmax (IU/mL)	1.004 ± 0.186	0.828 ± 0.269	0.753 ± 0.131	0.854 ± 0.202
Cmax.norm (IU/mL [IU/kg])	0.019 ± 0.004	0.019 ± 0.005	0.017 ± 0.003	0.016 ± 0.003

Parameter	Simoctocog alfa [CHR]	Previous FVIII [CHR]	Simoctocog alfa [OS]	Previous FVIII [OS]
IVR (% per IU/kg)	1.876 ± 0.354	1.848 ± 0.457	1.607 ± 0.288	1.591 ± 0.301
Tmax (h)	0.56 ± 0.30	0.74 ± 0.56	0.56 ± 0.29	0.73 ± 0.55
T1/2 (h)	9.73 ± 2.69	11.04 ± 2.50	12.50 ± 4.17	13.12 ± 3.03
MRT (h)	12.31 ± 3.85	13.70 ± 3.30	15.82 ± 5.51	16.92 ± 4.24
CL (mL/h/kg)	4.89 ± 1.95	4.76 ± 1.90	4.73 ± 1.87	4.46 ± 1.60
Vss (mL/kg)	54.90 ± 11.21	60.35 ± 13.79	67.18 ± 13.27	70.32 ± 15.78

Comment: *Based on the CHR assay*, the mean AUC and C_{max} valued for simoctocog alfa were higher than the corresponding values for the previously used FVIII concentrates, but when corrected for dose the mean AUC_{norm} and $C_{max.norm}$ values were almost identical for the two treatments. The mean IVRs for both treatments were similar, while the mean $T_{1/2}$, MRT and V_{ss} were slightly lower and the CL slightly higher for simoctocog alfa than for the previously used FVIII concentrates. T_{max} was reached within 30 minutes in 80.8% and 92.3% of patients after administration of previously used FVIII concentrates and simoctocog alfa, respectively. Previous pdFVIII concentrates had been used by 20 patients (19 with available CHR assay data), and previous rFVIII concentrates had been used by 6 patients (all full-length FVIII). The PK data varied according to the type of previously used FVIII concentrate. For example, for previously used rFVIII concentrates compared with previously used pdFVIII concentrates, higher values were obtained for AUC_{norm} (0.27 vs 0.23 h·IU/mL per IU/kg), IVR (2.224% vs 1.729% per IU/kg) and $T_{1/2}$ (11.64 vs 10.85 h). Simoctocog alfa values for these parameters were more like those of previously used pdFVIII concentrates than those of previously used rFVIII concentrates.

Based on the OS assay, PK values followed a similar pattern to those based on the CHR assay, with the exception of lower mean AUC and C_{max} values for simoctocog alfa compared with previously used FVIII concentrates. However, when corrected for dose the mean AUC_{norm} and $C_{max.norm}$ values were almost identical for simoctocog alfa and for previously used rFVIII concentrates. The T_{max} was reached within 30 minutes in 84.6% and 96.2% of patients after administration of previously used FVIII concentrates and simoctocog alfa, respectively. PK data for the previously used FVIII concentrate also varied according to the type of product. For example, for previously used rFVIII concentrates compared with previously used pdFVIII concentrates, higher values were obtained for AUC_{norm} (0.28 vs 0.24 h·IU/mL per IU/kg), IVR (1.797% vs 1.529% per IU/kg) and $T_{1/2}$ (14.18 vs 12.81 hours). The main PK parameters of simoctocog alfa were more like those of previously used pdFVIII concentrates than those of previously used rFVIII concentrates.

k. PK results (PK Cycles 1 and 2) - paediatric population subgroup aged 2-5 years

The PK parameters (mean±SD) for previous FVIII concentrates (PK Cycle 1) and simoctocog alfa (PK Cycle 2), as determined by the CHR and OS assays, are shown below in Table 8 for the sub-group of children aged 2-5 years.

Table 8: GENA-03 - PK parameters (mean±SD) for simoctocog alfa and previous FVIII concentrates measured by the CHR and OS assays; PK-PP population for the 2 - 5 years age group, n=13 and n=12 (CHR assay for previous FVIII product).

Parameter	Simoctocog alfa [CHR]	Previous FVIII [CHR]	Simoctocog alfa [OS]	Previous FVIII [OS]
AUC (h·IU/mL)	11.69 ± 5.30	8.68 ± 3.00	10.07 ± 4.60	10.83 ± 3.41
AUCnorm (h·IU/mL [IU/kg])	0.22 ± 0.10	0.20 ± 0.06	0.22 ± 0.10	0.21 ± 0.06
Cmax (IU/mL)	0.992 ± 0.148	0.746 ± 0.116	0.729 ± 0.088	0.797 ± 0.120
Cmax.norm (IU/mL [IU/kg])	0.019 ± 0.003	0.017 ± 0.002	0.016 ± 0.002	0.015 ± 0.002
IVR (% per IU/kg)	1.871 ± 0.270	1.683 ± 0.224	1.572 ± 0.167	1.513 ± 0.222
Tmax (h)	0.50 ± 0.00	0.75 ± 0.58	0.50 ± 0.00	0.73 ± 0.56
T1/2 (h)	9.49 ± 3.32	10.07 ± 2.90	11.91 ± 5.36	11.74 ± 3.03
MRT (h)	11.92 ± 4.93	12.35 ± 3.68	15.11 ± 7.35	15.03 ± 4.31
CL (mL/h/kg)	5.40 ± 2.37	5.65 ± 2.01	5.41± 2.32	5.23 ± 1.68
Vss (mL/kg)	55.32 ± 7.09	64.08 ± 9.60	68.29 ± 10.42	73.37 ± 16.53

Comment: *Based on the CHR assay*, the mean AUC, C_{max} and IVR values after administration of simoctocog alfa in the 2-5 age group were higher than the corresponding values for previously used FVIII concentrates, and this difference was still apparent when the AUC and C_{max} were normalised for dose. The mean $T_{1/2}$, MRT, CL and V_{ss} were all lower for simoctocog alfa than for the previously used FVIII concentrates. T_{max} following previously used FVIII concentrates was reached within 30 minutes in 76.9% of patients compared with 100% of patients following simoctocog alfa.

Based on the OS assay, the mean AUC and C_{max} values after administration of simoctocog alfa were lower than those of the previously used FVIII concentrates, but the difference between the two treatment groups was not apparent when the two parameters were corrected for dose. The mean $T_{1/2}$, MRT, IVR and CL were

slightly higher and V_{ss} lower for simoctocog alfa than for the previously used FVIII concentrates. T_{max} following previously used FVIII concentrates was reached within 30 minutes in 84.6% compared with 100% of patients following simoctocog alfa.

l. PK results (PK Cycles 1 and 2) - paediatric population subgroup aged 6-12 years

The PK parameters (mean±SD) for previous FVIII concentrates (PK Cycle 1) and simoctocog alfa (PK Cycle 2), as determined by the CHR and OS assays, are shown below in Table 9 for the sub-group of children aged 6-12 years.

Table 9: GENA-03 - PK parameters (mean±SD) for simoctocog alfa and previous FVIII concentrates measured by the CHR and OS assays; PK-PP population for the 6 - 12 years age group, n=13 and n=12 (for CHR assay for simoctocog alfa).

Parameter	Simoctocog alfa [CHR]	Previous FVIII [CHR]	Simoctocog alfa [OS]	Previous FVIII [OS]
AUC (h·IU/mL)	13.15 ± 3.43	12.69 ± 5.18	11.77 ± 2.72	15.62 ± 5.35
AUCnorm (h·IU/mL [IU/kg])	0.25 ± 0.06	0.28 ± 0.09	0.26 ± 0.06	0.29 ± 0.09
Cmax (IU/mL [IU/kg])	1.017 ± 0.225	0.903 ± 0.346	0.776 ± 0.164	0.911 ± 0.253
Cmax.norm (IU/mL)	0.019 ± 0.004	0.020 ± 0.006	0.017 ± 0.004	0.017 ± 0.004
IVR (% per IU/kg)	1.881 ± 0.440	2.000 ± 0.564	1.641 ± 0.377	1.669 ± 0.355
Tmax (h)	0.63 ± 0.43	0.73 ± 0.56	0.62 ± 0.42	0.73 ± 0.56
T1/2 (h)	9.99 ± 1.88	11.94 ± 1.73	13.08 ± 2.59	14.51 ± 2.41
MRT (h)	12.74 ± 2.34	14.95 ± 2.40	16.53 ± 2.87	18.82 ± 3.32
CL (mL/h/kg)	4.33 ± 1.21	3.93 ± 1.41	4.05 ± 0.92	3.69 ± 1.09
Vss (mL/kg)	54.45 ± 14.80	56.92 ± 16.42	66.07 ± 15.99	67.28 ± 15.01

Comment: *Based on the CHR assay*, AUC and C_{max} values were slightly higher for simoctocog alfa compared with previously used FVIII concentrates, but this was reversed after standardisation of the two parameters for dose. $T_{1/2}$, MRT and IVR were all slightly lower for simoctocog alfa compared with previously used FVIII concentrates, while CL was slightly higher for simoctocog alfa than for previously used FVIII concentrates. T_{max} was reached within 30 minutes following in 84.6% of patients both treatments.

Based on the OS assay, AUC and AUC_{norm} values were higher for previously used FVIII concentrates compared with simoctocog alfa. C_{max} values were higher for previously used FVIII concentrates compared with simoctocog alfa, but values for this parameter were similar for the two treatments after standardisation for dose. $T_{1/2}$, MRT, IVR and V_{ss} were all slightly lower and CL was higher for simoctocog alfa than for previously used FVIII concentrates. T_{max} was reached within 30 minutes in 84.6% of patients following previously used FVIII concentrates compared with 92.3% of patients following simoctocog alfa.

m. In vivo recovery (IVR) results for simoctocog alfa over time - CHR assay

Mean IVRs according to the CHR assay for all patients continuing onto or beginning prophylactic treatment (Phase II) in the ITT population are summarised below in Table 10. Doses administered for IVR analyses in the ITT population according to the CHR assay were 53.1±1.5 IU/kg at the start of Phase I, 52.7±2.9 IU/kg at the start of Phase II, 52.2±4.3 IU/kg at 3 months and 51.6±3.1 IU/kg at 6 months. In the PK-PP analysis population, according to the CHR assay, the mean±SD administered doses were 53.1±1.5 IU/kg at study start, 52.2±3.9 IU/kg at 3 months and 51.6±2.5 IU/kg at 6 months.

Table 10: GENA-03 - IVR values (%/IU/kg) for simoctocog alfa (CHR assay) over time; ITT population

Time-point	Group	n	Mean	SD	Median	Range
Start Phase I *	All patients	26 [a]	1.834	0.409	1.845	0.771–2.632
	Aged 2-5	13	1.871	0.270	1.822	1.530–2.426
	Aged 6-12	13 [a]	1.796	0.521	1.916	0.771–2.632
Start Phase II *	All patients	30 [b]	1.568	0.509	1.586	0.496–2.539
	Aged 2-5	14 [b]	1.446	0.457	1.563	0.496–2.011
	Aged 6-12	16	1.676	0.542	1.602	0.808–2.539
3 Months	All patients	55 [d]	1.698	0.402	1.682	0.880–2.811
	Aged 2-5	28	1.549	0.330	1.604	0.880–2.120
	Aged 6-12	27 [c]	1.852	0.418	1.805	1.068–2.811

Time-point	Group	n	Mean	SD	Median	Range
6 months	All patients	53 [e]	1.765	0.464	1.760	0.611–3.398
	Aged 2-5	26 [c]	1.672	0.396	1.709	0.611–2.535
	Aged 6-12	27 [c]	1.854	0.512	1.826	1.149–3.398

Note: [a] = data not available for 1 patient; [b] = data not available for 2 patients; [c] = data not available for 3 patients; [d] = data not available for 4 patients; [e] = data not available for 6 patients; data were not available for 2 patients (6–12 years) at 3 and 6 months due to premature withdrawal from the study; other missing IVR values were not evaluable. * = Phase I includes all patients who underwent PK analysis in Cycles 1 and 2; Phase II specifies recovery at start of open treatment phase and therefore includes only patients who did not undergo PK analysis.

Comment: In patients aged 2-12 years (ITT population), based on the CHR assay mean IVR values over time were above 1.5% per IU/kg, and ranged from 1.568% to 1.834% per IU/kg. The mean IVR values over time (ITT population) ranged from 1.446% to 1.871% per IU/kg in patients aged 2–5 years and from 1.676% to 1.854% per IU/kg in patients aged 6–12 years. In patients aged 2-12 years (PK-PP analysis population), based on the CHR assay mean IVR values over time ranged from 1.747% to 1.876% per IU/kg. The mean IVRs over time (PK-PP analysis population) ranged from 1.631% to 1.871% per IU/kg in patients aged 2–5 years, and from 1.772% to 1.885 % per IU/kg in patients aged 6–12 years. The mean IVR values over time for the PK-PP analysis population appeared to be more consistent compared with the corresponding values for the ITT population.

n. In vivo recovery (IVR) results for simoctocog alfa over time - OS assay

Mean IVRs according to the OS assay for all patients in the ITT population are summarised below in Table 11. Doses administered for IVR analyses in the ITT population according to the OS assay were 45.4±1.1 IU/kg at the start of Phase I (n=27), 45.0±2.7 IU/kg at the start of Phase II (n=32), 44.4±4.0 IU/kg at 3 months (n=57) and 43.9±2.7 IU/kg at 6 months (n=57). In the PK-PP analysis population, according to the OS assay, the mean±SD administered doses were 45.4±1.1 IU/kg at study start, 44.8±3.5 IU/kg at 3 months and 44.6±2.4 IU/kg at 6 months.

Table 11: GENA-03 - IVR values (% per IU/kg) for simoctocog alfa (OS assay) over time; ITT population

Time-point	Group	n	Mean	SD	Median	Range
Start Phase I *	All patients	27	1.575	0.327	1.594	0.748 – 2.239
	Aged 2-5	13	1.572	0.167	1.602	1.215–1.874
	Aged 6-	14	1.577	0.434	1.519	0.748–

Time-point	Group	n	Mean	SD	Median	Range
	12					2.239
Start Phase II *	All patients	31 [a]	1.419	0.357	1.454	0.650–2.159
	Aged 2-5	16	1.321	0.309	1.408	0.650–1.732
	Aged 6-12	15 [a]	1.523	0.385	1.528	0.666–2.159
3 Months	All patients	53 [d]	1.470	0.359	1.504	0.810–2.345
	Aged 2-5	29	1.350	0.268	1.388	0.810–1.747
	Aged 6-12	24 [d]	1.615	0.405	1.628	0.854–2.345
6 months	All patients	55 [c]	1.525	0.343	1.501	0.823–2.580
	Aged 2-5	28 [a]	1.441	0.296	1.456	0.823–2.096
	Aged 6-12	27 [b]	1.611	0.371	1.577	1.109–2.580

Note: [a] = data not available for 1 patient; [b] = data not available for 3 patients; [c] = data not available for 4 patients; [d] = data not available for 6 patients; data were not available for 2 patients (6–12 years) at 3 and 6 months due to premature withdrawal from the study; other missing IVR values were not evaluable. * = Phase I includes all patients who underwent PK analysis in Cycles 1 and 2; * Phase II specifies recovery at start of open treatment phase and therefore includes only patients who did not undergo PK analysis.

Comment: In the ITT population, based on the OS assay the mean IVR over time ranged from 1.419% to 1.575% per IU/kg in patients aged 2-12 years, 1.321% to 1.572 % per IU/kg in patients aged 2-5 years, and 1.523% to 1.615 % per IU/kg in patients aged 6–12 years. In the PK-PP population, based on the OS assay the mean IVR values over time ranged from 1.466% to 1.607 % per IU/kg in patients aged 2-12 years, 1.368% to 1.572% per IU/kg in patients aged 2–5 years, and 1.546% to 1.641% per IU/kg in patients aged 6–12 years. The mean IVRs for simoctocog alfa in the ITT and the PK-PP populations according to the OS assay were lower than those according to the CHR assay.

o. Conclusions relating to the PK data from study GENA-03

PK analysis was performed in a subset of 26 patients (13 aged 2–5 years; 13 aged 6–12 years) who were treated per-protocol after administration of their previously used FVIII concentrates (6 received pdFVIII and 20 received full-length rFVIII) and simoctocog alfa. In the PK-PP analysis population, for patients aged 2-12 years and for patients in the two age sub-groups,

mean FVIII:C (IU/mL) versus time post-infusion profiles were similar following previously used FVIII concentrates and simoctocog alfa standardised to 50 IU/kg in the cross-over analyses when assessed by both the CHR and the OS assays. The PK results described below relate to PK-PP analysis population using the CHR assay unless otherwise stated. The general pattern of the PK results as determined by the CHR assay was consistent with that determined by the OS assay.

In children aged 2-12 years, the PK parameters for simoctocog alfa and previously used FVIII concentrates were similar, and no marked differences between parameters were observed. The mean AUC_{norm} values simoctocog alfa and previously used FVIII concentrates were similar (0.23 and 0.24 h•IU/mL per IU/kg, respectively), while the mean $C_{max.norm}$ values for the two FVIII products were identical (both 0.019 IU/mL per IU/kg).

In children aged 2-5 years, the mean AUC_{norm} values for simoctocog alfa and previously used FVIII concentrates were similar (0.22 and 0.20 h•IU/mL per IU/kg, respectively), but for children aged 6-12 years mean AUC_{norm} values were higher for previously used FVIII concentrates than for simoctocog alfa (0.28 vs 0.25 h•IU/mL per IU/kg, respectively). The mean $C_{max.norm}$ values were similar for both simoctocog alfa and previously used FVIII concentrates in children aged 2-5 years (0.019 and 0.017 IU/mL per IU/kg, respectively), and in children aged 6-12 years (0.019 and 0.020 IU/mL per IU/kg, respectively). The mean AUC_{norm} for simoctocog alfa was slightly lower in children aged 2-5 years compared with children aged 6-12 years (0.22 vs 0.25 h•IU/mL per IU/kg, respectively), while the mean $C_{max.norm}$ for simoctocog alfa was identical for both age groups (0.019 IU/mL per IU/kg).

In children aged 2-12 years, the mean $T_{1/2}$ was shorter for simoctocog alfa than for previously used FVIII concentrates (9.7 vs 11.0 hours, respectively), while the mean CL was similar for both treatments (4.89 vs 4.76 mL/h/kg, respectively). In children aged 2-5 years, the mean $T_{1/2}$ was similar for simoctocog alfa and previously used FVIII concentrates (9.49 vs 10.07, respectively), as was the mean CL (5.40 vs 5.65 mL/min/kg, respectively). In children aged 6-12 years, the mean $T_{1/2}$ was about 2 hours shorter for simoctocog alfa than for previously used FVIII concentrates (9.99 vs 11.94 hours, respectively), while the mean CL was slightly higher (4.33 vs 3.93, respectively). The mean $T_{1/2}$ for simoctocog alfa was slightly shorter in the 2-5 years age group compared with the 6-12 years age group (9.49 vs 9.99 hours, respectively), while the mean CL for simoctocog alfa was higher (5.40 vs 4.33 mL/min/kg, respectively).

In children aged 2-12 years, T_{max} was reached within 30 minutes in 80.8% of patients following previously used FVIII concentrates and 92.3% of patients following simoctocog alfa. In children aged 2-5 years, T_{max} was reached within 30 minutes in 76.9% of patients following previously used FVIII concentrates and in 100% of patients following simoctocog alfa. In children aged 6-12 years, the percentage of patients reaching T_{max} within 30 minutes was identical following both previously used FVIII concentrates and simoctocog alfa (that is, 84.6%).

Recovery at baseline was evaluated in 27 patients participating in the PK analysis and for an additional 32 patients participating only in the prophylactic treatment efficacy analysis (Phase II), and all 57 patients were evaluated at 3 months and at 6 months. The following results are based on the CHR assay unless otherwise stated. In children aged 2-12 years, mean IVRs were above 1.5% per IU/kg at all time points (1.568% to 1.834% per IU/kg) in the ITT population, and above 1.7 % per IU/kg) at all time points (1.747% to 1.876% per IU/kg) in the PK-PP analysis population. In the ITT population, mean IVR values ranged from 1.446% to 1.871 % per IU/kg over the time points in patients aged 2-5 years and from 1.676% to 1.854 % per IU/kg over the time points in patients aged 6–12 years. In the PK-PP analysis population, mean IVR values ranged from 1.631% to 1.871% per IU/kg over the time points in patients aged 2-5 years, and from 1.772% to 1.885% per IU/kg over the time points in patients aged 6–12 years. Mean IVRs according to the OS assay were marginally lower than corresponding mean IVRs according to the CHR assay in both the ITT and PK-PP analysis populations.

3.4.3. GENA-08 - previously treated adult patients aged from 18 to 75 years

a. Title

Clinical Study To Investigate The Efficacy, Safety, And Immunogenicity Of Simoctocog alfa In Previously Treated Patients With Severe Haemophilia A.

b. Location

The study was conducted at 10 investigational centres in Austria (1 centre), Bulgaria (1 centre), Germany (3 centres) and the UK (5 centres). The Co-ordinating Investigator was located at the Experimental Haematology and Transfusion Medicine, Bonn, Germany. The study was conducted from 22 June 2010 to 31 January 2012, and the CSR was dated 19 July 2012. The study was conducted in accordance with standard ethical requirements.

c. Objectives

The *primary objective* of the study was to determine the efficacy of simoctocog alfa during prophylactic treatment, for the treatment of bleeding episodes (BEs), and for surgical prophylaxis, in PTPs with severe haemophilia A.

The *secondary objectives* of the study were: to calculate the incremental recovery of FVIII:C for simoctocog alfa; to investigate the immunogenic potential of simoctocog alfa; and to assess the safety of simoctocog alfa.

d. Design

GENA-08 was designed as a multinational, multicentre, Phase III study, to investigate the efficacy, safety and immunogenicity of simoctocog alfa in previously treated adult male patients with severe haemophilia A (FVIII:C ≤ 1%). The study enrolled 32 patients. After the first IVR assessment, patients entered the open-label, single-arm, treatment phase and treated with simoctocog alfa prophylactically (including surgery prophylaxis if required) and on-demand (in case of breakthrough bleeds) for a period of 6 months and at least 50 EDs. Two additional IVR assessments were scheduled at 3 months and 6 months. No assessment of standard PK parameters was undertaken in this study.

e. IVR assessments and statistical methods

For the IVR assessments, simoctocog alfa was administered at a dose of 50 IU FVIII/kg (exact amount according to labelled potency). The IVR was calculated at study entry (Visit 1) and after 3 and 6 months of treatment from the FVIII levels pre-infusion and the peak levels obtained in the 15, 30, 45 or 60 minutes post-infusion samples. Recovery was calculated based on the actual potency of simoctocog alfa according to the CHR and the OS assays. Recoveries over time were compared, and recovery was calculated according to the formula used in GENA-01 and GENA-03.

f. Chromogenic (CHR) and one-stage assays (OS)

FVIII:C measurements for determining IVR were performed using validated methods for the OS and CHR assays in the central laboratory, which also assigned the actual drug potency by means of the same assays. IVR was measured at the beginning of the study, after 3 months and at the end of the study (after 6 months). FVIII inhibitory and non-inhibitory antibodies were measured by validated methods in the central laboratory.

The statistical analysis of all endpoints was exploratory, and no confirmatory statistical analysis was planned. No formal sample size calculation was undertaken.

g. Demographics

The study enrolled 32 patients. IVRs were assessed in all patients who underwent at least one IVR assessment and included 32 patients at Visit 1, 31 patients at 3 months and 30 patients at 6 months. The mean±SD age of patients in the study (n=32) was 37.3±13.6 years (range: 18, 75

years), the mean height was 178.4±7.9 cm (range: 158, 192), the mean±SD weight was 82.5±18.0 kg (range: 47, 127), and 90.6% (n=29) of patients were white with the remaining 9.4% (n=3) of patients being Asian,

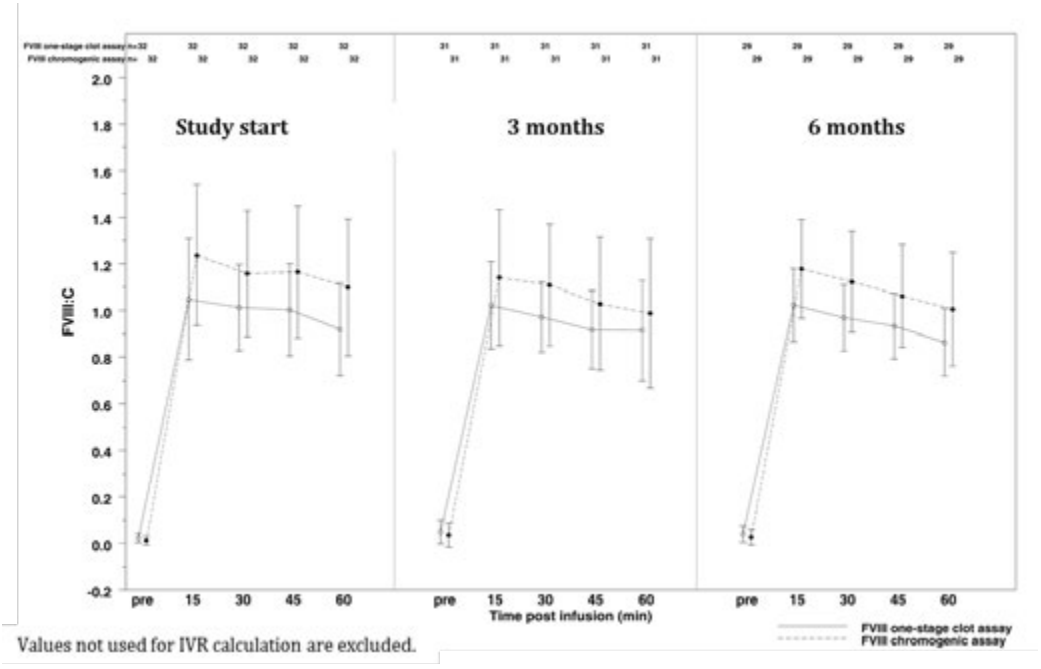
h. IVR results over time

The mean±SD (range) actual doses of simoctocog alfa administered for IVR determination according to the CHR and OS assays (respectively) in the ITT population were:

- Visit 1 (n=32), 55.6±2.8 IU/kg (range: 49.2, 61.6) and 47.8±2.8 IU/kg (range: 43.2, 54.7);
- 3 months (n=31), 53.5±4.6 IU/kg (range: 35.0, 59.2) and 45.1±4.2 IU/kg (range: 29.4, 51.7); and
- 6 months (n=30), 53.6±2.3 IU/kg (range: 49.1, 57.7) and 45.3±2.5 IU/kg (range: (40.7, 51.2).

The FVIII (mean±SD) (IU/L) concentrations over time as determined by the CHR and OS assays are summarised below in Figure 4. After the wash-out period and before the administration of simoctocog alfa, FVIII: C levels were low, as expected in this population. Mean concentrations increased at 15 minutes post-injection and remained elevated compared with baseline values at 60 minutes post injection, although a slight decrease in mean concentrations was observed between 15 and 60 minutes due to elimination of the infused FVIII. This pattern was consistently observed at all three time-point assessments, and there were no marked differences in either peak concentrations or the rate of decrease in FVIII concentration between 15 and 60 minute across the three time points. The comparative profiles for the CHR and OS assays showed that FVIII concentrations were higher when determined by the CHR assay compared with the OS assay during the elimination phase when standardised to actual dose of 50 IU/kg.

Figure 4: GENA-08 - FVIII (mean±SD) levels (IU/mL) during IVR assessment at Visits 1, 3 months and 6 months, standardised to actual 50 IU/kg dose; ITT population n=32.



FVIII:C = FVIII coagulant activity; ITT = intention-to-treat; IU = international units; IVR = in vivo recovery; SD = standard deviation.

The results for the IVR and $C_{max.norm}$ at the three time-points are summarised below in Table 12. IVR at Months 3 and 6 were similar, but recoveries at both of these time points were lower than Visit 1. As determined by the CHR assay, the Month 3 vs Visit 1 and Month 6 vs Visit 1 geometric

mean (% of Visit 1 recovery) for individual simoctocog alfa recoveries in the ITT population (n=32) were 93% (90% CI: 88.3, 97.7) and 90% (90% CI: 84.9, 96.1), respectively. As determined by the OS assays, the Month 3 vs Visit 1 and Month 6 vs Visit 1 geometric mean (% of Visit 1 recovery) for individual simoctocog alfa recoveries in the ITT population (n=32) were 94% (90% CI: 88.3, 100.1) and 91% (90% CI: 85.6, 96.9), respectively.

Table 12: GENA-08 - IVR and Cmax.norm parameters for simoctocog alfa; ITT population.

Time	Parameter	Mean	SD	Median	Range
Visit 1 (n=32)	IVR (% per IU/kg), CHR assay	2.57	0.54	2.61	1.46 – 3.68
	Cmax.norm (kg/mL), CHR assay	0.026	0.005	0.026	0.015 – 0.037
	IVR (% per IU/kg), OS assay	2.20	0.47	2.17	1.33 – 3.25
	Cmax.norm (kg/mL), OS assay	0.022	0.005	0.022	0.013 – 0.033
3 months (n=31)	IVR (% per IU/kg), CHR assay	2.37	0.50	2.29	1.36 – 3.54
	Cmax.norm (kg/mL), CHR assay	0.024	0.005	0.024	0.014 – 0.035
	IVR (% per IU/kg), OS assay	2.05	0.35	2.00	1.39 – 2.58
	Cmax.norm (kg/mL), OS assay	0.021	0.003	0.022	0.016 – 0.026
6 months (n=30)	IVR (% per IU/kg), CHR assay	2.34	0.40	2.35	1.63 – 3.08
	Cmax.norm (kg/mL), CHR assay	0.024	0.004	0.024	0.016 – 0.033
	IVR (% per IU/kg), OS assay	2.01	0.30	1.93	1.43 – 2.81
	Cmax.norm (kg/mL), OS assay	0.021	0.003	0.020	0.016 – 0.028

Comment: The 90% CIs for the geometric mean recoveries of simoctocog alfa (Month 3 vs Visit 1 and Month 6 vs Visit 1) were enclosed with the standard BE limits of 80% to 125%, based on both the CHR and the OS assays. These results suggest that the lower IVR observed at Months 3 and 6 compared with Visit 1 are unlikely to be clinically significant.

3.4.4. Supportive pharmacokinetics studies in patients with haemophilia A.

3.4.4.1. GENA-09 - adult patients aged 18 to 62 years

a. Title

Clinical Study to Investigate the Pharmacokinetics, Efficacy, Safety and Immunogenicity of Simoctocog alfa in Previously Treated Patients with Severe Haemophilia A.

b. Location

The study was conducted at 1 centre in Russia. The co-ordinating investigator was located at the Centre for Haematological Research, Russian Academy of Medical Science, Moscow, Russia. The study was conducted from 16 March to 26 May 2010, and the CSR was dated 14 December 2010. The study was conducted in accordance with standard ethical requirements.

c. Objectives

The primary objective of the study was to determine the PK profile of simoctocog alfa in terms of FVIII coagulant activity (FVIII:C) and to compare it with the FVIII:C profile of a full-length rFVIII in previously treated patients (PTPs) with severe haemophilia A (FVIII:C ≤1%).

The secondary objectives of the study were: to calculate the incremental recovery of FVIII:C for simoctocog alfa; to investigate the immunogenic potential of simoctocog alfa; to assess the clinical efficacy and safety of simoctocog alfa during prophylactic treatment; to assess the clinical efficacy and safety of simoctocog alfa in the treatment of breakthrough BEs; and to assess the clinical efficacy and safety of simoctocog alfa in surgical prophylaxis.

d. Design

GENA-09 was the first clinical study designed to investigate simoctocog alfa for the treatment of severe haemophilia A. It was designed as a prospective, open-label, single-centre, Phase II study in patients with severe haemophilia A (FVIII:C ≤1%). It included a randomised cross-over PK part (Part I) and an uncontrolled prophylaxis part (Part II).

In the PK phase (Part I, PK1), the PK properties of simoctocog alfa and a licensed recombinant FVIII concentrate BHK were studied. Two clinic visits were required for PK assessments (Cycle 1 and Cycle 2). Each cycle was preceded by a wash-out period of at least 96 hours in patients who were not actively bleeding. The second PK cycle was to follow within one week of the first cycle (including the 96-hour wash-out). Patients were randomised to receive either simoctocog alfa or the rFVIII comparator in Cycle 1 and to receive the alternate treatment in Cycle 2. Samples were taken for FVIII inhibitor and anti-FVIII antibody analysis before administration of either FVIII product.

Patients were randomised to one of two treatment sequences (simoctocog alfa followed by the rFVIII comparator or vice versa). The treatments consisted of 50 IU FVIII/kg (labelled potency) of simoctocog alfa (Part 1 [PK] and recovery analysis [months 3 and 6]) and the rFVIII comparator (Part 1 [PK] only). The doses for the first PK investigation were administered within 4 weeks after the screening visit and were only postponed in case of a BE. The second PK dose was administered directly after the first one (i.e. within 1 week including the 96-hour washout period), unless a postponement was required due to a BE.

Patients who completed Part 1 of the study (PK phase) were then able to enter Part II of the study (efficacy and safety phase) for a period of 6 months and at least 50 EDs with simoctocog alfa as prophylaxis for BEs. In addition, patients were also treated with simoctocog alfa on-demand for breakthrough BEs and could receive simoctocog alfa prophylaxis for surgical procedures.

Comment: In this first clinical study, WFI for reconstitution of the freeze-dried powder was provided in vials as pre-filled syringes were not available for this study. From late 2009 onwards, sterilised WFI was provided for all further clinical studies in

prefilled syringes.

e. Pharmacokinetic assessments and associated statistical methods

PK analysis for both full-length rFVIII BHK and simoctocog alfa were undertaken in Cycles 1 and 2 of Part I. Actual potency was used for calculating PK parameters to account for differences between lots. All PK calculations (except T_{max}) were based on the actual sampling times and not on the nominal time points. FVIII:C values below the limit of quantification were set to 0 for PK calculations.

The primary PK endpoint was the comparison of AUC for FVIII:C between simoctocog alfa and full-length rFVIII BHK using both the CHR and the OS assays. *The secondary PK endpoints* were incremental IVR, $T_{1/2}$, maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), mean residence time (MRT), volume of distribution at steady state (V_{ss}) and CL.

The geometric mean ratio with 90% CI of simoctocog alfa over full-length rFVIII BHKwas used to compare selected primary and secondary PK parameters. The ratios were calculated using standard methods. A supportive analysis of AUC and IVR using a standard cross-over ANOVA model was performed in order to provide estimates adjusted for possible patient, sequence and period effects.

For the PK analysis, FVIII levels were measured before and 0.25, 0.5, 0.75, 1, 3, 6, 9, 12, 24, 30 and 48 hours after the end of the infusion. The incremental IVR was calculated from plasma FVIII:C levels before infusion and from peak plasma FVIII:C levels obtained in the 0.25, 0.5, 0.75, or 1 hour post-infusion samples. The same formula was used to calculate the IVR as used for GENA-01, GENA-03 and GENA-08.

For patients who entered Part II of the study (efficacy and safety phase), IVR for simoctocog alfa was measured at 3 months (PKREC-3M population). Full PK analysis for simoctocog alfa was performed in patients at 6 months (PK2-6M population) who had undergone full PK analysis in Part I.

No formal size calculation was performed. The sample size (n=22) was chosen to satisfy applicable CHMP and FDA recommendations.

The primary analysis population for the PK data (Part 1) was the PK-PP population. The PK-PP population included all randomised patients who completed Part I of the study receiving both treatments without significantly violating the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the PK results. PK data were also analysed in the PK-6 months PP population (PK-6m-PP) consisting of all patients admitted to the study who completed the PK analysis 6 months after start without significantly violating the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the PK results.

f. Chromogenic (CHR) and one-stage (OS) assays

FVIII:C measurements (OS and CHR) assays were undertaken in a central laboratory located in the USA (same laboratory as used for samples from GENA-01 and GENA-03). If required for pre-, intra- and post-surgery samples for FVIII:C were measured locally.

g. Demographic

A total of 22 patients were enrolled in this study. There were no premature discontinuations. All 22 patients were included the ITT population for PK assessments. The PP population in for the PK analysis in Part 1 included all 22 patients, and the PP populations at 3 and 6 months included 21 patients (data for one patient were excluded due to an implausible concentration-time profile after the 6-month PK infusion). In the submitted CSR, the PK data focused primarily on the CHR assay it was stated that this is the accepted measure in Europe and Russia.

The mean±SD age of the 22 male patients in the study at the time of the first treatment with

simoctocog alfa was 24.5±9.77 years (range: 18, 62 years), the mean ± weight was 69.0±13.82 kg (range: 50, 105 kg), and all patients were white Caucasian.

Comment: The sponsor commented that the adult patients in this study differed from the adult patients in the other two other clinical studies (GENA-01, GENA-08) in that the Russian patients had been "inadequately treated in the past, as evidenced by the high total HJHS at study start (mean 45.3, median 45.0)".

h. PK results - actual dose

The mean± SD actual doses (CHR assay) during the first PK assessment were 49.9±1.6 IU/kg for simoctocog alfa and 54.7±0.5 IU/kg for full-length rFVIII BHK. The actual dose (IU/kg) of simoctocog alfa was approximately 9% lower than that of full-length rFVIII BHK.

The mean± SD actual doses (OS assay) during the first PK assessment were 40.0±1.7 IU/kg for simoctocog alfa and 54.2±0.5 IU/kg for full-length rFVIII BHK. The actual dose (IU/kg) of simoctocog alfa was approximately 26% lower than that of full-length rFVIII BHK.

i. PK results - FVIII plasma concentrations over time

FVIII-C levels (IU/L, mean±SD) versus time profiles through to 48 hours and dose standardised to 50 IU/kg, as determined by both CHR and OS assays, for the PK1-PP population were provided. The FVIII:C profiles for both simoctocog alfa and full-length rFVIII BHK, standardised to dose, were similar for the two products according to both the CHR and OS assays,

j. PK results (PK1)

Mean±SD primary and secondary PK parameters for simoctocog alfa and full-length rFVIII BHK, as determined by the CHR and OS assays, in the PK1-PP population are summarised below in Table 13.

Table 13: GENA-09 - Primary and secondary PK parameters (mean±SD) for simoctocog alfa and full-length rFVIII BHK according to the CHR and OS assays: PK1-PP population; n=22.

Parameter	Simoctocog alfa [CHR]	full-length rFVIII BHK [CHR]	Simoctocog alfa [OS]	full-length rFVIII BHK [OS]
AUC (h·IU/mL)	14.73 ± 5.97	17.95 ± 6.09	11.75 ± 5.22	19.85 ± 6.90
AUCnorm (h·IU/mL per IU/kg)	0.29 ± 0.12	0.33 ± 0.11	0.29 ± 0.13	0.37 ± 0.13
Cmax (IU/mL)	1.097 ± 0.159	1.199 ± 0.216	0.889 ± 0.230	1.159 ± 0.198
Cmax.norm (IU/mL per IU/kg)	0.022 ± 0.003	0.022 ± 0.004	0.022 ± 0.005	0.021 ± 0.004
IVR (% per IU/kg)	2.172 ± 0.281	2.166 ± 0.393	2.190 ± 0.555	2.111 ± 0.386
Tmax (h)	0.38 ± 0.20	0.49 ± 0.26	0.38 ± 0.21	0.38 ± 0.19
T1/2 (h)	11.11 ± 2.98	13.45 ± 3.39	11.43 ± 3.94	16.16 ± 5.88

Parameter	Simoctocog alfa [CHR]	full-length rFVIII BHK [CHR]	Simoctocog alfa [OS]	full-length rFVIII BHK [OS]
MRT (h)	14.68 ± 4.10	17.62 ± 4.57	15.80 ± 5.63	21.52 ± 7.56
CL (mL/h/kg)	3.86 ± 1.39	3.38 ± 1.09	3.94 ± 1.44	3.06 ± 1.06
Vss (mL/kg)	52.25 ± 10.72	55.77 ± 10.42	55.82 ± 8.94	59.41 ± 9.62

The geometric mean ratios for AUC_{norm} (h•IU/mL per IU/kg) for simoctocog alfa over full-length rFVIII BHK were 88% (90% CI: 81.9, 95.6), according to the CHR assay, and 78% (90% CI: 72.7, 84.5), according to the OS assay, when calculated by ANOVA. The geometric mean ratios (90% CI) for selected PK parameters were provided.

Comment: The mean values for AUC were notably lower for simoctocog alfa than for full-length rFVIII BHK as determined by both the CHR and OS assays, and were particularly striking for the OS assay. The differences between the two products were reduced after the AUC was dose normalized, but are still noteworthy. In order to account for these findings, the sponsor states that GENA-09 was the first clinical study to be conducted with simoctocog alfa and at the beginning of the study only 500 IU vials were available. When assayed by the CHR method these 500 IU vials contained, on average 500 IU of simoctocog alfa, while when assayed by the OS method these 500 IU vials contained on average 400 IU of simoctocog alfa. As doses for the PK assessments were calculated based on nominal potency, patients received only around 40 IU/kg instead of the planned 50 IU/kg based on the OS actual potency. FVIII:C values assed by the OS assay in samples taken towards the end of the PK assessment were close to, or below, the detection limit. Several PK parameters depend on these late FVIII:C values for their calculation (for example, $T_{1/2}$ depends mainly on the elimination rate, which is determined by linear regression on the terminal phase of the FVIII:C measurement; and MRT, CL and Vss depend on AUC). Therefore, the sponsor comments that the determination of those parameters based on late FVIII:C values determined by the OS assay "was probably compromised. It is noteworthy that, with the exception of Vss, these were precisely the parameters that were not within the bioequivalence range, whereas bioequivalence could be demonstrated for parameters depending on early FVIII:C measurements, such as IVR and $C_{max.norm}$".

k. PK results over time - study time vs 6 months

For the second PK assessment at 6 months, the actual simoctocog alfa dose administered was 49.0±1.0 IU/kg as measured by the CHR assay and 41.1±2.0 IU/kg as measured by the OS assay. Overall, the PK parameters for simoctocog alfa at 6 months were consistent with those at study start. All 90% CIs for the ratios of geometric means for PK parameters at 6 months were enclosed within the accepted bioequivalence range of 80% to 125% for both assays, although some 90% CIs did not include 100% (that is, $T_{1/2}$ and MRT for both assays and AUC, AUC_{norm}, IVR and $C_{max.norm}$ for the OS assay). The 90% CIs for the geometric mean ratios (6 months/start) for all key PK parameters for simoctocog alfa were enclosed within the limits of 80% to 125%.

l. IVR values

At the study start, the geometric mean ratios for IVR (% per IU/kg) for simoctocog alfa over full-length rFVIII BHKwere 101% (90% CI: 93.5%, 109.6%), according to the CHR assay, and 103% (90% CI: 93.2%, 113.0%), according to the OS assay, when calculated by ANOVA. The results for

both assays showed that the 90% CI for the IVR ratios for both FVIII products were within the standard bioequivalence interval of 80% to 125%.

Mean±SD IVRs for simoctocog alfa were comparable for both the CHR and OS assays at study start (2.17±0.28% vs 2.19±0.56% per IU/kg, respectively). However, at both 3 and 6 months the IVR values were higher with the CHR assay than with the OS assay: 3 months (2.09±0.44% vs 1.73±0.32% per IU/kg, respectively), and 6 months (2.29±0.57% vs 1.97±0.50% per IU/kg, respectively). The geometric mean ratios for IVR (% per IU/kg) for simoctocog alfa at 6 months relative to study start were 107% (90% CI: 99.1%, 114.9%), according to the CHR assay, and 92% (90% CI: 85.3%, 99.1%), according to the OS assay. Overall, the results for IVR over time for simoctocog alfa suggest that the observed changes observed with both the CHR and OS assays are unlikely to be clinically significant.

3.4.5. GENA-04 (extension study of GENA-09)

GENA-04 was the extension study of GENA-09. Of the 22 patients enrolled in the parent study, 18 enrolled in the extension study. In this study, the IVR was assessed at 3 months and subsequently every 3 months until study completion (terminated after a mean of 226 EDs per patient). No assessment of standard PK parameters was undertaken in this study.

The IVR was calculated after a wash-out phase of at least 72 hours before the infusion. FVIII plasma level pre-infusion and the peak level obtained in the 30 or 60 minutes post-infusion samples were used for the calculation. All 18 patients underwent at least one IVR assessment and were included in the analysis comparing baseline data (that is, end of GENA-09) with study completion data (that is, end of GENA-04). The actual doses of simoctocog alfa administered for IVR assessments at baseline and study completion according to the CHR assay were 48.93±1.0 IU/kg and 50.45±3.4 IU/kg, respectively, and the corresponding actual doses according to the OS assay were 40.89±2.1 IU/kg and 44.26±2.9 IU/kg, respectively.

At baseline (n=18), the mean±SD IVRs according to the CHR and OS assays were 2.024±0.680% and 1.715±0.525% per IU/kg, respectively, and at completion (n=16), the corresponding results for the IVRs were 2.023±0.483% and 1.699±0.382% per IU/kg. The IVR was lower at each time point when determined by the OS assay compared with the CHR assay. However, IVR values were consistent from baseline through to at least 15 months.

3.5. Comparison of PK results across studies

The results for the key PK parameters for simoctocog alfa and comparator FVIII products across studies were summarised and provided.

3.6. Evaluator's overall conclusions on pharmacokinetics

The PKs of simoctocog alfa have been satisfactorily characterised in previously treated adults and children aged 2-12 years with severe haemophilia A (FVIII:C ≤ 1%). The submission included five clinical studies with PK data for simoctocog alfa. The primary PK data were provided in GENA-01 (22 adult patients[1]), GENA-03 (26 children aged 2 to 12 years), and GENA-08 (32 adult patients). The supportive PK data were provided in two studies in adults, GENA-09 (n=22) and its extension GENA-04 (n=18). Studies GENA-01, GENA-03 and GENA-09 included comprehensive PK data, while studies GENA-08 and GENA-04 provided data relating to IVR. No patients in the five clinical studies had FVIII inhibitors at study entry. All patients in the five studies were males, and were predominantly "white". There were no PK data in patients younger than 2 years of age. There were no PK data in previously untreated patients. There were no PK studies specifically in adolescents aged > 12 years to ≤ 18 years, or in patients aged ≥ 65 years.

[1] Age range 12-65

In all studies, the FVIII products were administered at a dose of 50 IU/kg (labelled potency). FVIII:C plasma levels were determined by validated CHR and OS assays undertaken by the same central laboratory located in the USA. Actual potencies as determined by the CHR and OS assays were used to calculate PK parameters. For simoctocog alfa, FVIII:C values obtained by the OS assay were about 15% lower than those obtained by the CHR assay. However, the OS assay results for full-length rFVIII products (5 lots of full-length rFVIII BHK FS in GENA-01 and 3 lots in GENA-03, one lot each of third generation full-length rFVIII (CHO) and first-generation full-length rFVIII (CHO) in GENA-03) were approximately 15% higher than the CHR assay results, except for one lot of full-length rFVIII BHK in GENA-09, where there was no difference between the OS and CHR assays.

In GENA-01, the mean FVIII:C levels standardised to a dose of 50 IU/kg were comparable over time (to 48 hours) for simoctocog alfa and "licensed" FS full-length rFVIII BHK, as measured by both the CHR and OS assays. In this study, simoctocog alfa and "licensed" full-length rFVIII BHK KS were bioequivalent based on the 90% CI for the geometric ratio of AUC_{norm} (CHR and OS assays) for the two products being within the standard bioequivalence limits of 0.80 to 1.25. Overall, the key PK parameters assessed in Part 1 (PK phase) of GENA-01 were similar for simoctocog alfa and "licensed" full-length rFVIII BHK, as measured by both the CHR and OS assays. The main difference in the PK parameters between the two FVIII products was the shorter mean half-life observed with simoctocog alfa compared with "licensed" full-length rFVIII BHKobserved with both assays (14.7 vs 16.1 hours [CHR assay]; 17.1 vs 18.8 hours [OS assay]).

In GENA-09, supportive data for the bioequivalence of simoctocog alfa and full-length rFVIII BHK were provided based on the 90% CI of the geometric ratio for the AUC_{norm} (CHR assay) for the two products being within the standard bioequivalence limits. However, the 90% CI of the geometric ratio for the AUC_{norm} for the two products was not enclosed entirely within the standard bioequivalence limits of 0.80 to 1.25 when the parameters were assessed by the OS assay. The sponsor comments that the potencies of the simoctocog alfa batches used in GENA-09 were approximately 20% lower than labelled when assessed by the OS assay. Consequently, FVIII:C levels measured by the OS assay in samples taken late in the elimination phase were close to, or below, the detection limit resulting in imprecise assessment of those PK parameters which are dependent on accurate levels taken during this period (for example, AUC, $T_{1/2}$, and CL). In addition, the sponsor states that the adult patient population in GENA-09 differed from that in GENA-01 as the patients appeared to have been inadequately treated in the past as evidenced by the presence of severely affected joints and historically high bleeding rates. Furthermore, all patients included in GENA-09 were from a single Russian centre, while patients included in GENA-01 were from multiple centres predominantly in Western Europe.

In both GENA-01 and GENA-09, PK parameters for simoctocog alfa at 6 months were assessed, and in general were consistent with the corresponding values obtained at the start of the study when measured by the CHR assay. However, when measured by the OS assay the differences in the key PK parameters between month 6 relative to study start were more marked than when measured by the CHR assay (particularly in GENA-09). In GENA-01 (CHR assay), the 90% CIs for the geometric ratios for the key PK parameters at month 6 relative to study start were within the standard bioequivalence interval of 0.80 to 1.25, apart from $T_{1/2}$ and MRT which were both shorter at month 6 than at study start. In GENA-01 (OS), the 90% CIs for the geometric mean ratios for the key PK parameters at month 6 relative to study start were within the standard bioequivalence interval of 0.80 to 1.25, apart from AUC_{norm} (lower at month 6), and $T_{1/2}$ and MRT (both shorter at month 6).

In GENA-03, the PKs of simoctocog alfa were compared with previously used FVIII concentrates (recombinant and plasma derived) in children aged 2-12 years. In children aged 2-12 years (n=25), the AUC_{norm} and $C_{max.norm}$ values were almost identical for simoctocog alfa and previously used FVIII concentrates when measured by both the CHR and OS assays. However, the mean

AUC_{norm} (CHR assay) for simoctocog alfa was slightly lower in the 2-5 years age cohort compared with the 6-12 years age cohort (0.22 vs 0.25 h•IU/mL per IU/kg, respectively), while the mean $C_{max.norm}$ (CHR assay) was identical for both age cohorts (0.019 IU/mL per IU/kg). In addition, the mean $T_{1/2}$ (CHR assay) for simoctocog alfa was slightly shorter in the 2-5 years age cohort compared with the 6-12 years age cohort (9.49 vs 9.99 hours, respectively), while the mean CL was higher (5.40 vs 4.33 mL/min/kg, respectively).

In children aged 2-12 years (n=25) in GENA-03, the mean AUC_{norm} (CHR assay) at study start with simoctocog alfa was lower than in the adult population (n=22) in GENA-01 (0.23 vs 0.39 h•IU/mL per IU/kg, respectively), while the mean $T_{1/2}$ was shorter (9.73 vs 14.73 hours, respectively) and the mean CL was higher (4.89 vs 2.94 mL/h/kg, respectively). The observed PK differences between children and adults were not unexpected, and the sponsor notes that these differences have been observed with other FVIII products. In *Bjorkman et al (2010)*, IVR was lower, weight-adjusted clearance was higher and FVIII half-life was lower in children with severe haemophilia A (aged 1-6 years of age) than in older patients (aged 10-65 years).[7]

The IVR was assessed in all studies and was generally consistent across the studies. In GENA-08 (CHR assay), the mean±SD IVR in adult patients at visit 1 (n=32) was 2.57±0.54% per IU/kg, and this value was consistent with values at month 3 (n=31) and month 6 (n=30) of 2.37±0.50% per IU/kg and 2.34±0.40% per IU/kg, respectively. The IVR (CHR assay) was also generally consistent over time in adult patients in GENA-01, GENA-09 and GENA-04. In GENA-03 (CHR assay), the mean±SD IVR at the start of the study in children aged 2-12 years (n=25) was notably lower than in adult patients (n=22) in GENA-01 (CHR assay), with the respective values being 1.83±0.41% per IU/kg and 2.50±0.37% per IU/kg. The IVR (CHR assay) was consistent over time in the paediatric population aged 2-12 years in GENA-03 (that is, start, 3 months, 6 months). The sponsor comments that lower IVR values have been observed in children compared with adults with other FVIII products.[7] However, the lowed FVIII recovery in children compared with adults suggests that higher doses of simoctocog alfa might be required in children compared with adults to treat haemophilia and this was in fact observed in the clinical efficacy data.

There were no PK studies in humans relating to metabolism, excretion, hepatic impairment, renal impairment or drug-drug interactions. However, FVIII is a well characterised coagulation factor and a normal constituent of human plasma. Consequently, it can be reasonably anticipated that the metabolism, excretion, PKs in hepatic impairment, PKs in renal impairment and PK drug-drug interactions of simoctocog alfa is unlikely to differ from endogenous FVIII. There were no PK studies in females, in elderly patients (≥ 65 years of age), or in patients from different racial groups. However, the absence of PK data for simoctocog alfa in these patient groups is not considered to be a critical issue.

4. Pharmacodynamics

The pharmacodynamics of simoctocog alfa appear to have been extensively investigated in the preclinical data.

5. Dosage selection for the pivotal studies

The simoctocog alfa dosage used in all five clinical studies for PK assessment was 50 IU FVIII/kg according to the labelled potency. This dose is in accordance with published guidelines for the design and analysis of pharmacokinetic studies of FVIII.[4] In each of the clinical studies, assessment of efficacy and safety followed on from the PK assessment.

In the two pivotal studies assessing simoctocog alfa for prophylaxis, the dose in adults was 30-40 IU FVIII/kg every day until 6 months and at least 50 days had been reached (GENA-08), and

the dose in children was 30-40 IU FVIII/kg every other day or 3 times weekly, with two dose escalations of +5 IU/kg each allowed in case of inadequate response defined as ≥ BEs during one month.

In the three pivotal studies (GENA-01, GENA-08, GENA-03), the simoctocog alfa dose for treating BEs depended on the severity of bleeding. For minor BEs, the dose was 20–30 IU FVIII/kg every 12–24 hours until BE resolution. For major BEs the dose was 30–40 IU FVIII/kg, repeated every 12–24 hours until BE resolution. For major to life-threatening BEs the initial dose was 50–60 IU FVIII/kg with subsequent doses of 20–25 IU FVIII/kg every 8–12 hours until BE resolution.

In the three pivotal studies (GENA-01, GENA-08, GENA-03), the simoctocog alfa dose for prophylaxis during surgical procedures depended on whether the procedure was minor or major. For minor procedures (including tooth extraction), the dose was 25–30 IU FVIII/kg within 3 hours prior to surgery to achieve peak target level of ~50–60%, repeated every 12–24 hours until healing is complete. Trough level to be maintained at ~30%. For major surgical procedures, the dose was 50 IU FVIII/kg within 3 hours prior to surgery to achieve target peak level of ~100%, repeated if necessary after 6–12 hours initially and for ≥6 days until healing is complete. Trough level to be maintained at ~50%.

6. Clinical efficacy

6.1. Studies providing clinical efficacy data

The sponsor nominated three, multicentre, multinational studies as providing primary efficacy data (GENA-01, GENA-08 and GENA-03), and two, single-centre studies as providing supportive efficacy data (GENA-09 and its extension GENA-04). The five studies have been fully evaluated and studies GENA-01, GENA-08 and GENA-03 are considered to be the pivotal efficacy and safety studies, while studies GENA-09 and GENA-04 are considered to the supportive efficacy and safety studies. The five studies are outlined below in Table 14.

Table 14: Five studies providing efficacy data.

Study	Design	Patients	Primary objectives	Secondary objectives
GENA-01 Phase II Pivotal	Phase II, prospective, randomised, active-controlled, open-label, multi-centre. Start: 27/04/2012 End: 18/09/2012.	22 adult PTPs enrolled: all 22 in ITT and SAF populations, and 14 in the PP population	• Determine the PKs of simoctocog alfa and compare with PKs of a full-length rFVIII BHK	• Calculate incremental recovery; • Investigate immunogenicity; • Assess clinical efficacy and safety in the treatment of BEs and in surgical prophylaxis.
GENA-08	Phase III, prospective,	32 adult PTPs	• Determine the efficacy	• Calculate incremental

Study	Design	Patients	Primary objectives	Secondary objectives
Phase III Pivotal	multinational, multicentre, open-label, single-arm. Start: 22/07/2010. End: 31/01/2012.	enrolled: all 32 in ITT and SAF populations;	of simoctocog alfa during prophylactic treatment, treatment of BEs and in surgical prophylaxis.	recovery; • Investigate immunogenicity; • Assess safety.
GENA-03 Phase III Pivotal	Phase III, prospective, multinational, multicentre, open-label, non-controlled. Start: 27/12/2010. End: 06/11/2012.	59 paediatric PTPs enrolled; all 59 patients were analysed for efficacy; patients aged from 2 to 12 years (inclusive).	• Assess clinical efficacy of simoctocog alfa in terms of prevention & treatment of (breakthrough) BEs.	• Determine PKs; • Determine incremental recovery; • Investigate immunogenicity; • Assess efficacy in surgical procedures; • Assess safety by AE monitoring.
GENA-09 Phase II Supportive	Phase II, prospective, single-centre, open-label, randomised cross-over PK part and uncontrolled efficacy part. Start: 16/03/2009. End: 26/05/2010.	22 adult PTPs enrolled: all 22 were included in the analyses (safety, ITT, PROPH populations).	• Determine the PKs of simoctocog alfa and compare with previously used a full-length rFVIII BHK.	• Calculate incremental recovery. • Investigate immunogenicity. • Assess clinical efficacy and safety during prophylactic treatment. • Assess clinical efficacy and safety for treatment of breakthrough BEs. • Assess clinical

Study	Design	Patients	Primary objectives	Secondary objectives
				efficacy and safety in surgical prophylaxis.
GENA-04 Phase IIIb Supportive	Phase IIIb extension study to GENA-09 to investigate long-term safety and efficacy. Start: 21/11/2009. End: 28/07/2011.	18 adult patients who completed GENA-09; all 18 patients included in the ITT efficacy and the safety population, and 16 in the PP population.	• Determine long-term immunogenic potential of simoctocog alfa. • Assess long-term tolerability of simoctocog alfa.	• Determine long-term efficacy of simoctocog alfa during prophylactic treatment, for treatment of breakthrough BEs, and for prophylaxis during surgical procedures. • Calculate long-term incremental recovery of FVIII.

6.2. Pivotal efficacy studies

6.2.1. GENA-01 (Phase II study) - PTPs adolescent and adults (12-65 years)

6.2.1.1. Study design, objectives, locations and dates

GENA-01 was designed as a prospective, randomised, actively-controlled, open-label, cross-over, multicentre, Phase II study in previously treated patients (PTPs) with severe haemophilia A (FVIII:C ≤ 1%). The study was undertaken in Bulgaria (1 site), Germany (2 site) and the USA (6 sites), between 27 May 2010 and 18 September 2012. The CSR was dated 15 February 2013. The principal/co-ordinating investigator was located at the Hemophilia and Thrombosis Center, University of Colorado Denver, USA. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and ICH-GCP (Note for Guidance CPMP/ICH/135/95), and national regulatory requirements. The study was sponsored by Octapharma AG, Switzerland.

The **primary objective** of the study was to determine the pharmacokinetics (PKs) of simoctocog alfa based on FVIII coagulant activity (FVIII:C) and to compare them with the PKs of a full-length rFVIII BHK concentrate in PTPs with severe haemophilia A.

The **secondary objectives** of the study were: to calculate the incremental recovery of FVIII:C for simoctocog alfa; to investigate the immunogenic potential of simoctocog alfa; to assess efficacy and safety of simoctocog alfa for the treatment of bleeding episodes (BEs); and to assess clinical efficacy and safety of simoctocog alfa in surgical prophylaxis

The study included two parts and enrolled 22 PTPs. In Part I (PK phase), the PK properties of simoctocog alfa and the full-length rFVIII concentrate were studied. In Part II (efficacy phase),

patients who completed Part I were followed up for at least 6 months or until 50 exposure days (EDs) were reached, whichever came last. Because there were 2 patients who had only infrequent bleeding, the protocol was amended to stipulate that the study would end by the end of September 2012 even if these two patients had not reached 50 EDs. During Part II, the effects of on-demand treatment with simoctocog alfa on bleeding episodes (BEs) was documented, and the PKs of simoctocog alfa were assessed at 6 months in those subjects with Part I PK data. In subjects who underwent surgical procedures, all relevant treatment details were to be documented. Safety and immunogenicity were monitored throughout the study.

During the screening visit, inclusion and exclusion criteria were checked, informed consent was obtained, and demographic data and patient baseline characteristics, as well as results of a general physical examination, including the assessment of the Haemophilia Joint Health Score (HJHS) according to *Hilliard et al 2006*[11] were recorded (range 0 [best] to 148 [worst]). In addition, medical history, vital signs, height and body weight (BW) were documented. Patients were also instructed on how to document treatment details and record haemostatic efficacy, adverse events (AEs) and concomitant medication in the patient diary provided. FVIII:C (by CHR and OS assay), FVIII inhibitor level and anti-rhFVIII antibodies were measured at screening, and blood samples for FVIII inhibitor and anti-rhFVIII antibody measurements were to be taken not less than 72 hours after the last FVIII administration. Safety laboratory tests (haematology, chemistry, electrolytes and urinalysis) were analysed at screening and CD4+T cells measured. Verification was also required establishing that patients were HIV negative or, if positive, had a viral load of <200 particles/µL or <400,000 copies/mL.

The PK analyses have been described in the *Pharmacokinetics* section of this CER. All patients who completed Part I of the study continued with on-demand treatment with simoctocog alfa. The start of Part II (efficacy Phase) was defined as the first day after the last PK sample had been taken during PK Cycle 2. Patients received a sufficient amount of simoctocog alfa for home treatment, to be used for on-demand treatment of BEs. However, short periods of prophylactic treatment were permitted beyond the resolution of the acute phase to prevent recurrent haemorrhage, for example following a major surgery or following certain major BEs, or iliopsoas bleeds or bleeding into target joints.

The first visit (interim visit 1) in Part 2 of the study was to be undertaken when patients reached 10 to 15 EDs after the start of therapy with simoctocog alfa. Patients who reached 10 to 15 EDs before the scheduled 3-month visit were to have only inhibitor and anti-rhFVIII antibody testing at the 10 to 15 ED visit. If the ED 10 to 15 visit fell within the 2-week period prior to the scheduled 3-month visit, then the ED 10 to 15 visit was omitted and only the 3-month visit procedures were performed. The 3-month (± 2 weeks) visit included measurement of BW, inhibitor and anti-rhFVIII antibody testing and IVR analysis. This visit was to be undertaken not less than 72 hours after the previous administration of simoctocog alfa. At this visit, vital signs were to be analysed before and 1 hour after administration of simoctocog alfa, and safety laboratory measurements were to be carried out before simoctocog alfa administration.

The 6-month (+ 2 weeks) visit consisted of a full PK analysis with simoctocog alfa following a wash-out phase of at least 96 hours. FVIII inhibitor levels and anti-FVIII antibodies were measured before simoctocog alfa administration, vital signs were recorded before and 1, 24 and 48 hours after simoctocog alfa administration and safety laboratory measurements were taken before and 24 hours (excluding urinalysis) and 48 hours after simoctocog alfa administration. The 6-month visit was also the study completion visit for subjects who had at least 50 EDs documented for simoctocog alfa treatment. In this case a general physical examination and urinalysis were to be performed.

Patients with less than 50 EDs at the 6-month visit point were to have additional visits every 3 months until achievement of 50 EDs. These visits were for the purpose of inhibitor and anti-rhFVIII antibody testing, and were to be undertaken not less than 72 hours after the last

administration of simoctocog alfa. Completion visits for these patients were to take place once 50 EDs had been reached or by the end of September 2012. The same assessments as for the 6-months visit (except PK assessment) took place at this time point. The investigations undertaken at the 3- and 6-month visits and at the completion visit were provided. For patients undergoing surgical interventions, treatment details were documented for the pre-, intra-, and postoperative phase.

If inhibitor development was suspected (for example, unexplained need to increase dose, study product infusions non-efficacious, prolonged bleeds) additional FVIII inhibitor and anti-rFVIII antibody tests were performed. Other reasons for unscheduled visits were the occurrence of serious adverse events (SAEs) or hospitalisations because of severe BEs or because of a surgical intervention. AEs and use of concomitant medication were documented throughout the study. Patient diaries, including any BEs, treatment of BEs, concomitant medications and AEs, were reviewed and data transferred to the CRF.

Efficacy and safety data (including inhibitor data) were monitored by an Independent Data Monitoring Committee (IDMC). The IDMC was composed of recognised experts in the field of haemophilia clinical care who were not actively recruiting subjects.

6.2.1.2. Inclusion and exclusion criteria

The **inclusion criteria** were:

1. Severe haemophilia A (FVIII:C ≤1%; historical value as documented in patient records).
2. Male patients ≥ 12 and ≤ 65 years of age.
3. Body weight 25 kg to 110 kg.
4. Previously treated with FVIII concentrate, at least 150 EDs.
5. Immunocompetent (CD4+ count >200/µL).
6. Negative for anti-HIV; if positive, viral load < 200 particles/µL or < 400,000 copies/mL.
7. Freely given written informed consent.

The **exclusion** criteria were:

1. Other coagulation disorder than haemophilia A.
2. Present or past FVIII inhibitor activity (≥ 0.6 Bethesda Units [BU]).
3. Severe liver or kidney disease (ALT and AST levels > 5 times of upper limit of normal; creatinine>120 µmol/L).
4. Receiving or scheduled to receive immuno-modulating drugs (other than antiretroviral chemotherapy) such as alpha-interferon, prednisone (equivalent to >10 mg/day), or similar drugs.
5. Participation in another interventional clinical study currently or during the past month.
6. In addition to the inclusion and exclusion, the study included standard criteria relating to withdrawal from therapy or assessment with adequate procedures for follow-up.

6.2.1.3. Treatment in the efficacy phase

- **On-demand treatment**

The dosage (and duration) of treatment of spontaneous or traumatic breakthrough BEs during the open label treatment period depended on the location and extent of bleeding and on the clinical situation. The required dosage was determined using the following formula:

> Required units = BW (kg) * desired FVIII rise (%) (IU/dL) * 0.5 (assuming that the recovery of FVIII is 2%/[IU/kg])

The required target peak levels were approximately:

- 40–60% in case of minor haemorrhage.
- 60–80% in case of moderate to major haemorrhage.
- 100–120% in case of major to life threatening BEs.

The following dosages were recommended:

- Minor haemorrhage (superficial muscle or soft tissue and oral bleeds): 20–30 IU FVIII/kg every 12–24 hours until BE resolution.
- Moderate to major haemorrhage (haemorrhage into muscles, into oral cavity; haemarthrosis; known trauma): 30–40 IU FVIII/kg, repeated every 12–24 hours until BE resolution.
- Major to life threatening BEs (intracranial, intra-abdominal, gastro-intestinal or intrathoracic bleeds, central nervous system bleeds, bleeding in retropharyngeal spaces or iliopsoas sheath, eyes/retina, fractures or head trauma): an initial dose of 50–60 IU FVIII/kg and subsequently a dose of 20–25 IU FVIII/kg every 8–12 hours until BE resolution.

No continuous infusions of simoctocog alfa were used for on-demand treatment of BEs, and all treatments were administered by bolus injection.

- **Surgical prophylaxis**

The dosage and duration of treatment with simoctocog alfa depended on the type of surgery and the patient's individual incremental recovery. The required dosage was determined using the following formula:

Dose = target increase of FVIII (IU/dL) * BW/actual IVR (IU/dL)/(IU/kg).

Additionally the following dosages were recommended:

- Minor surgeries including tooth extractions: 25–30 IU FVIII/kg within 3 hours prior to surgery to achieve an intended target peak level of about 50–60%, repeated every 12–24 hours until healing was complete. Trough level was to be maintained at approximately 30% (samples taken prior to the next infusion of simoctocog alfa).
- Major surgeries: 50 IU FVIII/kg within 3 hours prior to surgery to achieve an intended target peak level of approximately 100%, repeated if necessary after 6–12 hours initially and subsequently for at least 6 days until healing was complete. Trough levels were to be maintained at approximately 50% (samples taken prior to the next infusion of simoctocog alfa).

No continuous infusions of simoctocog alfa were used for surgical prophylaxis, and all treatments were administered by bolus injection.

- **Prior and concomitant treatment**

Treatment details concerning the FVIII concentrate used for the 6 month period before study entry were documented. Concomitant administration of therapies not interfering with the objectives of the study was permitted. No other FVIII concentrate was permitted, except for emergency situations and in case of treatment of bleedings occurring between screening and end of PK Cycle 2. Patients who switched to another FVIII product during the study were not considered treatment failures in the efficacy analyses if: (i) the use of another FVIII concentrate was due to an emergency; (ii) simoctocog alfa was not available for the patient in time. Immunomodulating drugs other than antiretroviral chemotherapy, such as α-interferon, prednisone (equivalent to >10 mg/day) or similar drugs were not permitted. Antifibrinolytics during surgery were not permitted unless it could not be avoided.

- **Treatment compliance**

Detailed procedures were put into place in order to assess treatment compliance. These procedures have been examined and are considered to be satisfactory.

6.2.1.4. Efficacy variables and outcomes

6.2.1.4.1. Bleeding episodes (BEs)

6.2.1.4.1.1. Details of the BEs

For all BEs occurring during the study the following data were documented by the patient (together with the investigator in case of on-site treatments) in the patient diary. Patients who experienced a major or life-threatening BE should preferably have been treated at the study site.

- Type of bleeding (spontaneous, traumatic, post-operative, other).
- Site of bleeding.
- Start date and time of occurrence/of noticing the bleed.
- Severity of the bleed (minor, moderate, major or life threatening).
- End date and time of BE. If the treatment of a BE at one site was interrupted for more than 48 hours, the events were recorded as two separate BEs. If another site than the original bleeding site was affected, the events were recorded as separate BEs at any time. If a patient experienced simultaneously BEs at several sites, each event was documented as a separate BE.
- Efficacy response assessment after each infusion of simoctocog alfa.
- Efficacy assessment at the end of the BE.
- Details of dose(s) and batch number used to treat BE were documented including increased and decreased doses of simoctocog alfa used to treat individual BEs (frequency and relative magnitude of dose changes); changes in the doses per infusion and changes in the total dose used to treat subsequent BEs of the same type (for example, elbow, knee, etc.) in the same patient (frequency and relative magnitude of dose changes).
- Dates and times of study product injections.

6.2.1.4.2. Efficacy assessment of the BE

After each infusion of simoctocog alfa and at the end of a BE, the following efficacy assessment was made by the patient (together with the investigator in case of on-site treatment):

- ***Excellent:*** Abrupt pain relief and/or unequivocal improvement in objective signs of bleeding within approximately 8 hours after a single infusion.
- ***Good:*** Definite pain relief and/or improvement in signs of bleeding within approximately 8 to 12 hours after an infusion requiring up to 2 infusions for complete resolution.
- ***Moderate:*** Probable or slight beneficial effect within approximately 12 hours after the first infusion requiring more than two infusions for complete resolution.
- ***None:*** No improvement within 12 hours, or worsening of symptoms, requiring more than 2 infusions for complete resolution.

For certain major bleeding events it may have been necessary to continue treatment beyond the resolution of the acute phase for a brief period of prophylaxis to prevent recurrent haemorrhage. These additional infusions had to be recorded separately and were not evaluated for efficacy.

A formal statistical test was to be performed to determine whether the proportion of BEs with successful treatment (rated as good or excellent at the efficacy assessment at end of BE) was significantly higher than 70%

6.2.1.4.3. Surgical prophylaxis

6.2.1.4.3.1. Surgical procedures

For all surgical procedures, the following data were documented:

- Location and type (planned or emergency) of surgery.
- Severity of surgery (minor - major, definitions see below).
- Expected duration of surgical procedure.
- Actual BW prior surgery (kg).
- Actual duration of surgical procedure (start and end times, that is, skin to skin).
- Pre-, intra-, and post-operative FVIII plasma levels.
- Expected and actual blood loss.
- All wound haematomas were to be captured, analysed, and reported noting whether they required surgical evacuation.
- FVIII inhibitor level and anti-rhFVIII antibodies pre-infusion.
- Laboratory tests (haematology, chemistry: before and 24 hours after end of surgery).
- Details on concomitantly administered products including any blood/blood product transfusions but excluding drugs given for routine anaesthesia.
- Details of administered dose(s) of simoctocog alfa given pre-, intra- and/or post-operatively (definitions see below) including dates, times, and batch number
- A brief narrative describing the outcome and efficacy of the intervention
- Overall efficacy assessment at the end of surgical prophylaxis by the surgeon and the haematologist.
- Monitoring of AEs.

6.2.1.4.4. Classification of surgeries

The classification of surgeries was made prospectively. Surgeries were defined as major if any of the following criteria were met (all other surgeries were defined as minor): (i) general or spinal anaesthesia; (ii) opening into the great body cavities in the course of which severe haemorrhage was possible; (iii) haemostatic therapy for at least 6 days; (iv) orthopaedic interventions involving joints (ankle, knee, hip, wrist, elbow, shoulder); (v) 3rd molar extraction or extraction of 3 or more teeth; or (vi) life-threatening surgeries/conditions.

6.2.1.4.5. FVIII plasma levels

FVIII plasma levels (CHR and OS assays, local and central laboratory) were documented for the following time-points: (i) immediately (<30 minutes) before and 60±15 min after pre-operative injection of study product; (ii) immediately (<30 minutes) before and 60±15 min after each intra-operative bolus dose (if any); and (iii) immediately (<30 minutes) before and 60±15 min after each post-operative dose (if any); in case of major surgery: mandatory for the first 3 post-operative doses.

6.2.1.4.6. Estimation of blood loss

*Prior to surg*ery, the surgeon was to provide written estimates of the volume (mL) of average and maximal expected blood loss for the planned surgical procedure for the same procedure in a subject with normal haemostasis, of the same sex, age, and stature. *Following surgery*, the actual blood loss was estimated by the surgeon.

6.2.1.4.7. Definitions of pre-, intra-, and post-operative blood loss

(i) *Pre-operative:* Any infusion given within 3 hours before start of surgery; (ii) *Intra-operative:* Any infusion given during surgery; and (iii) *Post-operative:* Any administration given following the final suture of the surgical incision until at least 2 days (minor surgery) or at least 6 days (major surgery) after surgery or until healing was complete, whichever occurred later, and the patient returned to his regular treatment. Short periods of prophylactic treatments were permitted following a major surgery.

6.2.1.4.8. Efficacy assessments

Efficacy was to be assessed at the end of surgery by the surgeon and post-operatively by the surgeon and the haematologist using the following criteria.

- ***Intra-operative efficacy:***
  - ***Excellent:*** Intra-operative blood loss was lower than or equal to the average expected blood loss for the type of procedure performed in a patient with normal haemostasis and of the same sex, age, and stature.
  - ***Good:*** Intra-operative blood loss was higher than average expected blood loss but lower or equal to the maximal expected blood loss for the type of procedure in a patient with normal haemostasis.
  - ***Moderate:*** Intra-operative blood loss was higher than maximal expected blood loss for the type of procedure performed in a patient with normal haemostasis, but haemostasis was controlled.
  - ***None:*** Haemostasis was uncontrolled necessitating a change in clotting factor replacement regimen.
- ***Post-operative efficacy*:**
  - ***Excellent:*** No post-operative bleeding or oozing that was not due to complications of surgery. All postoperative bleeding (due to complications of surgery) was controlled with simoctocog alfa as anticipated for the type of procedure.
  - ***Good:*** No post-operative bleeding or oozing that was not due to complications of surgery. Control of post-operative bleeding due to complications of surgery required increased dosing with simoctocog alfa or additional infusions, not originally anticipated for the type of procedure.
  - ***Moderate:*** Some post-operative bleeding and oozing that was not due to complications of surgery; control of post-operative bleeding required increased dosing with simoctocog alfa or additional infusions, not originally anticipated for the type of procedure.
  - ***None:*** Extensive uncontrolled post-operative bleeding and oozing. Control of post-operative bleeding required use of an alternate FVIII concentrate.
- ***An overall efficacy assessment*** taking both the intra- and post-operative assessment into account was to be done by the surgeon and the haematologist. The conclusion of the post-operative phase of a major surgery was defined as the date of discharge or post-operative Day 6, whichever occurred later.

6.2.1.5. Randomisation and blinding methods

The efficacy phase of the study was open-label and all patients received simoctocog alfa for on-demand treatment of BEs and/or surgical prophylaxis.

6.2.1.6. Analysis populations

The Intention-to-Treat (ITT) population was considered to be the most relevant for the evaluation of efficacy, and the Per-Protocol (PP) population was used to assess the robustness of the efficacy results in the ITT population.

The study included four basic analysis populations and these are outlined below:

- ***Safety analysis population (SAF):*** All patients who received at least one dose of simoctocog alfa.
- ***Intention-to-Treat (ITT):*** All patients in the safety analysis population for whom any data were collected post-treatment with simoctocog alfa.
- ***Efficacy - Per-Protocol (PP):*** All patients in the ITT analysis population who completed the study without significantly violating the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the efficacy results. Objective criteria for exclusion from the PP populations were defined prior to database lock.
- ***PK-PP population (PK-PP):*** All randomised subjects who completed Phase I (PK phase; cross-over) of the trial receiving both treatments without significantly violating the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the PK results.

In addition to the four basic analysis populations, the following study populations were defined:

- *PK-6 months PP population (PK-6m-PP):* All subjects admitted to the study who completed the PK assessment 6 months after start without significantly violating the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the PK results.
- *Population of BEs (BLEED and BLEED-PP):* All documented BEs of patients in the ITT population (BLEED) or PP population (BLEED-PP) for which any amount of treatment with simoctocog alfa was documented and which started between initiation of home treatment after PK Cycle 2 (that is, one day after drawing of last blood sample for PK) and the completion visit.
- *Surgery population (SURG and SURG-PP):* All documented surgical interventions in patients in the ITT population (SURG) or the PP population (SURG-PP) for which any amount of simoctocog alfa prior to, during or after surgery was documented and no other FVIII concentrate was documented within 24 hours prior to surgery.
- *Infusions analysis population (Safety-INF):* All documented infusions with simoctocog alfa to patients of the SAF population.

6.2.1.7. Sample size

The planned sample size chosen for this study was 20 to 25 patients. The sample size was selected to satisfy current FDA and CHMP recommendations relating to PK studies.

For the secondary hypothesis relating to the proportion of BEs successfully treated with on-demand simoctocog alfa (see below under *Statistical* methods), assuming independent binomially distributed success within patients and centres, the expected 1000 bleeding events shows that the rate of successful treatments (haemostatic efficacy rated good or excellent) is above 70% (α=0.025, one sided) if the true success rate is 75% or better with a power of at least 94%.

6.2.1.8. Statistical methods

The statistical methods relating to the primary PK analysis have been discussed in the *Pharmacokinetics* section of this CER.

The secondary efficacy analysis of on-demand treatment focused on the proportion of BEs with successful treatment (rated as good or excellent in the efficacy assessment at the end of the BE). An episode was considered as treatment failure if the efficacy assessment was moderate or none or if another FVIII product was used (except for emergency, in which case the episode was excluded from analysis). Unexplained blood transfusions also constituted a reason to consider an episode as treatment failure.

The formal statistical test was whether the proportion of successfully treated BEs was significantly higher than 70%. The null hypothesis was - H0: *p*success ≤ 0.7; and the alternative hypothesis was -H1: *p*success > 0.7, where *p*success represents the overall proportion of successfully treated BEs.

A 2-sided 95% Clopper-Pearson CI was calculated for the estimate of *p*success. On-demand treatment was claimed to be efficient if the lower confidence limit of the CI was > 0.7. In a secondary analysis, similar CIs were calculated for the different severity types of bleeding (minor, moderate, major).

As a secondary hypothesis, the proportion (*p*success1-2) of BEs that could be resolved with 1 or 2 infusions of simoctocog alfa was to be assessed, and a test of H0: *p*success1-2 ≤ 0.8 versus H1: *p*success1-2 > 0.8 was performed, using a 2-sided 95% Clopper-Pearson CI. This test was considered as supportive evidence for the primary hypothesis if the lower limit of the CI was > 0.8.

The frequency of BEs, the number of infusions needed to treat a BE, the number of EDs and study drug consumption data (FVIII IU/kg per infusion, per BE, per month, per year) per subject and in total were evaluated. In addition, increased and decreased doses of simoctocog alfa used to treat individual BEs (frequency and relative magnitude of dose changes), changes in the doses per infusion and changes in the total dose used to treat subsequent BEs of the same type (e.g. elbow, knee, etc.) in the same subject (frequency and relative magnitude of dose changes) were evaluated.

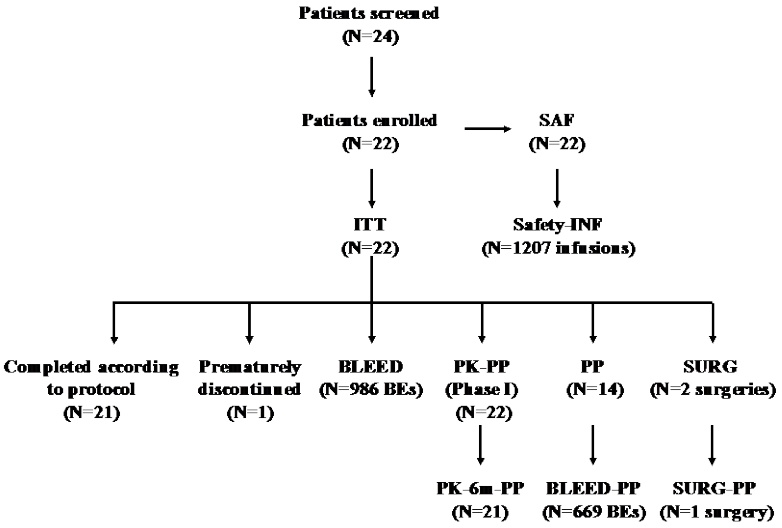
In general, missing values were not replaced. In the case of missing body weight, the last available weight measurement was used for calculation of recovery and the other PK parameters (last observation carried forward). If treatment efficacy evaluation for a BE was missing, the event was considered as not successfully treated in the ITT analysis and was excluded from the PP analysis.

An administrative interim analysis was performed after all subjects had completed the cross-over PK phase. In addition, an analysis of the efficacy data regarding on-demand treatment was provided, as well as a listing of AEs. The data from the interim analysis were reviewed at the 5th meeting of the IDMC for the GENA studies on 25 November 2011 and the interim data were sent to the FDA on 27 September 2012.

6.2.1.9. Participant flow

The patient disposition is summarised below in Figure 5.

Figure 5: GENA-01 - Patient disposition.



BE = bleeding episode; BLEED = study population of BEs treated with simoctocog alfa; ITT = intention-to-treat; PK = study population of patients undergoing PK analysis; PK-6m = study population of patients undergoing PK analysis at 6 months; PP = per-protocol; SAF = study population of patients in safety analysis; Safety-INF = study population of simoctocog alfa infusions; SURG = study population of surgeries treated with simoctocog alfa.

Comment: No patients discontinued the study due to AEs. One patient discontinued prematurely due to loss to follow-up. His last visit was 291 days after entering the study (9-month visit). Up to that point he had received 27 administrations (including PK analyses) and a total dose of 82,950 IU of simoctocog alfa.

6.2.1.10. Major protocol deviations

Of the 22 enrolled patients, 4 patients (18.2%) had major protocol deviations due to each of these patients using other FVIII products after the start of on-demand treatment. Three (3) of these 4 patients treated a total of 6 BEs with other FVIII products during the study because simoctocog alfa was not available, and in an additional 6 BEs in 1 patient because he felt that it was inconvenient to administer 10 vials of simoctocog alfa. The fourth patient returned all used and unused simoctocog alfa and instead treated himself with another rFVIII because he erroneously thought that he had completed the study, when in fact he still had to come back for the 6 month PK visit. None of these 4 patients were excluded from the PK-PP population as it was decided at the data review meeting that the deviations would have only minor potential to bias PK results. Eight (8) patients were excluded from the PP population evaluated for efficacy. These included the 4 patients described above due to the use of other FVIII products; one of these 4 patients additionally had less than 50 EDs during the on-demand phase. A further 4 patients (including the one that was lost to follow-up) were excluded from the PP efficacy population for having less than 50 EDs during the on-demand phase

6.2.1.11. Baseline data

The basic demographic characteristics of the 22 patients in the ITT/SAF are summarised below in Table 15.

Table 15: GENA-01 - Demographic characteristics of the study population (ITT/SAF); n=22.

Parameter	Mean	SD	Median	Range
Age (years)	39.6	14.06	41.0	12-65
Height (cm)	174.0	9.41	176.0	154-188
Weight (kg)	72.7	15.55	69.5	46-105
BMI (kg/m^2)	23.9	4.79	23.0	19-36
HJHS (Gait)	1.6	1.59	1	0-4
HJHS (Total)	38.4	30.29	31.5	0-84

HJHS = Haemophilia Joint Health Score; ITT = intention-to-treat; SAF = study population of patients in safety analysis; SD = standard deviation.

The majority of patients (18/22; 81.8%) were white, with the remainder being black or African American (3/22; 13.6%) or American Indian or Alaska Native (1/22; 4.5%). Known FVIII gene defects were documented for 4 out of 22 patients and all were single occurrence (intron-22 inversion, inversion type II, large deletion/insertion, stop mutation). A family history of haemophilia was documented in more than half of the patients (14/22; 63.4%), and two patients (9.1%) had a family history of inhibitor activity.

FVIII inhibitor levels were less than 0.6 BU in 16 patients at screening, as measured by both the Bethesda and the Nijmegen assays and in 6 (27.3%) patients FVIII inhibitors could not be determined at screening due to the remaining FVIII levels in plasma being too high for the inhibitor test to give a reliable result. However, all 6 of these patients had negative inhibitor values pre-infusion at PK Cycle 1.

The main historical bleeding sites were the ankle (54.5% [12/22] of patients both sides, 9.1% [2/22] each for left and right ankle), the knee (45.5% [10/22] of patients both sides, 9.1% [2/22] and 22.7% [5/22] left and right knee, respectively) and the elbow (40.9% [9/22] of patients both sides, 13.6% [3/22] and 27.3% [6/22] left and right elbow, respectively).

Full information on the total number of EDs for pre-study use of FVIII concentrate was available for 11 patients: 4 had received pdFVIII concentrates with a mean of 26.0 EDs and 7 had received rFVIII concentrates with a mean of 17.9 EDs within 6 months before the study start.

Six (6) patients were HIV-positive, all with $CD4^+$ T cell counts higher than 200/µL and the HIV viral load as measured by PCR well below 400,000 copies/mL.

6.2.1.12. Efficacy outcomes - bleeding episodes

6.2.1.12.1. Frequency and sites of BEs

In total, 997 BEs occurred after the start of home treatment. Of these, 986 BEs occurred in patients in the ITT population for which all treatments with simoctocog alfa were documented and which started between initiation of home treatment after PK cycle 2 (that is, one day after drawing of last blood sample for PK) and the completion visit.

Of the 986 BEs with documented simoctocog alfa treatment, 642 (65.1%) were spontaneous, 341 (34.6%) were traumatic, and 3 (0.3%) were due to other causes. In total there were 416 (42.2%) minor, 566 (57.4%) were moderate to major, 3 (0.3%) were major to life-threatening, and the severity for 1 BE was unknown.

The number of BEs treated with simoctocog alfa per patient ranged from 15 to 93. The most common sites of bleeding were the knee (230 BEs 23.3%), the elbow (225 BEs, 22.8%), other sites (166 BEs, 16.8%) and the ankle (155 BEs, 15.7%). Less common sites of bleeding were the

arm (99 BEs, 10.0%), the leg (71 BEs, 7.2%), the oral cavity (20 BEs, 2.0%), the nose (BEs, 1.5%), and the intestine (BEs 5, 0.5%).

Two (2) of the 3 major to life-threatening BEs were traumatic bleeds in the right elbow of one patient occurring within 5 days of each other. The first BE was treated with 3 infusions on 2 EDs with a total of 7000 IU (104.5 IU/kg) of simoctocog alfa with moderate efficacy. The second BE was treated with 2 infusions over 2 EDs with 5500 IU (82.1 IU/kg) of simoctocog alfa with good efficacy. The third major to life-threatening BE was a spontaneous right and left groin bleed in one patient. It required only 1 infusion of simoctocog alfa (4000 IU; 45.5 IU/kg) and efficacy was judged as good.

6.2.1.12.2. Treatment of bleeding episodes

The mean±SD duration of treatment of all BEs was 1.1±0.75 days (range: 1, 19 days). Minor BEs required a mean±SD of 1.0±0.17 days of treatment, moderate to major BEs a mean±SD of 1.2±0.96 days and major to life-threatening mean±SD of 1.7±0.58 days. The one BE that was of unknown severity (spontaneous bleed in the right forearm in one patient) required 2 days of treatment.

A total of 920 BEs were considered for the analysis of dose and number of infusions/EDs. All BEs in the BLEED population (n=986) were treated with at least one dose of simoctocog alfa. However, in cases where several bleedings were treated with the same set of infusions simultaneously, the number of infusions and the dosages were included only once per severity or site and efficacy assessment.

The number of infusions/EDs and the dosage for simoctocog alfa in the BLEED population are summarised below in Table 16. The median number of infusions for BEs was 1.0 (mean±SD 1.1±0.59; range 1, 13). The majority of BEs required only 1 simoctocog alfa infusion (841/986, 91.4%), while 53 BEs (5.8%) required 2 infusions. Twenty (2.2%) BEs required 3 infusions, 3 (0.3%) BEs required 4 and 2 (0.2%) BEs required 5 infusions, and 1 (0.1%) BE required 13 infusions. The median dose of simoctocog alfa per infusion for treatment of BEs was 30.0 IU/kg (range: 7, 61) across all severities; 29.9 IU/kg for minor BEs, 30.0 IU/kg for moderate to major BEs, and 33.9 IU/kg for major to life-threatening BEs. The BE of unknown severity was treated with 53.5 IU/kg. The median total dose of simoctocog alfa used for the treatment of a BE was 30.9 IU/kg (range 8, 657).

Table 16: GENA-01 - EDs and simoctocog alfa (*Simoctocog alfa/Human-cl rhFVIII*) dosage for treatment of BEs; BLEED population, n=986.

Parameter	Mean	SD	Median	Range
Number of infusions per bleeding site*	1.1	0.59	1.0	1-13
Dose of *Human-cl rhFVIII* per infusion, IU	2375	1055	2000	500-6000
Dose of *Human-cl rhFVIII* per infusion, IU/kg	32.3	10.59	30.0	7-61
Number of EDs per BE*	1.1	0.55	1.0	1-13
Dose of *Human-cl rhFVIII* per BE, IU	2693	2618	2000	500-65,000
Dose of *Human-cl rhFVIII* per BE, IU/kg	36.6	27.64	30.9	8-657

* Dosage used to treat several simultaneous bleedings are counted only once in this analysis. BE = bleeding episode; BLEED = study population of BEs treated with simoctocog alfa; ED = exposure day; IU = international unit; SD = standard deviation.

6.2.1.13. On-demand efficacy outcomes

Personal efficacy assessments were available for 985 BEs and missing for 1 BE. Overall, 94.4% (931/986) of all BEs were treated with excellent (60.3%, 595/986) or good (34.1%, 336/986) efficacy, while moderate efficacy was recorded for 5.5% (54/986) and for no BEs was efficacy reported as "none". Efficacy outcomes for BEs according to severity are summarised below in Table 17.

Table 17: GENA-01 - Efficacy rating - severity of BE (number of BEs).

Efficacy rating	Any (n=986) *	Minor (n=416)	Moderate to Major (n=566)	Major to life-threatening (n=3)
Excellent	595 (60.3%)	312 (75.0%)	283 (50.0%)	-
Good	336 (34.1%)	98 (23.6%)	236 (41.7%)	2 (66.7%)
Moderate	54 (5.5%)	6 (1.4%)	47 (8.3%)	1 (33.3%)
None	--	-	-	-
Missing	1 (0.1%)	-	-	-

* BEs = 986 (severity rating for 1 event was missing).

The proportion of BEs with successful treatment (rated as “good” or “excellent”; efficacy assessment at end of BE) was 94.4% (931/986 BEs) with a 95% CI of 92.8% to 95.8%. The lower 95% CI for the rate of successfully treated BEs was >70%, which meets the study's pre-specified primary criteria for treatment efficacy. The rate of BEs successfully treated with 1 or 2 infusions was 96.8% (954/986 BEs) with a 95% of CI 95.4% to 97.8%. This result supports the primary hypothesis as the lower 95% CI for the rate of BEs successfully treated with 1 or 2 infusions was > 80% (that is, pre-specified efficacy criteria).

The highest success rate was observed for minor BEs (98.6% [95% CI: 96.9, 99.5]), with a slightly lower rate for moderate to major BEs (91.7% [95% CI: 89.1, 93.8]) and the lowest rate for major to life-threatening BEs (66.7% [95% CI: 9.4, 99.2]) However, the number of major to life-threatening BEs (3 BEs) is too low to draw firm conclusions about the efficacy of simoctocog alfa for the treatment of these bleeds.

The success rate for patients treated per-protocol (BLEED-PP population) supported the success rate for the primary analysis in the ITT population (BLEED population), demonstrating the robustness of the efficacy results for simoctocog alfa for the treatment of BEs. In the BLEED-PP population, the overall success rate was 97.6% (653/669 BEs) with a 95% CI of 96.1% to 98.6%. The success rate for BEs treated with 1 or 2 infusions was 98.2% (657/669 BEs) with a 95% CI of 96.9% to 99.1%.

Efficacy assessments were also undertaken for each individual infusion and the results were similar to those for the personal efficacy assessments. The number of infusions assessed in the BLEED population was 1041, and 90.4% (n=941) of these infusions were judged as having excellent or good efficacy (48.2% excellent, 42.2% good), while efficacy was judged as moderate in 8.5% (n=88) of infusions and as none in 0.9% (n=9) of infusions. Efficacy assessment was missing for 3 infusions. The 9 infusions judged as having no efficacy were all administered for

moderate to major BEs, and 6 of these infusions were administered for 2 BEs in one patient (both for trauma to the right knee) while 3 were administered to one patient for a single BE (right side of the ribs, unclear whether the patient was treating the bleeding or the pain due to coughing).

6.2.1.14. Efficacy outcomes - surgical prophylaxis

During the study, 2 patients underwent 2 surgical procedures, one major and one minor. The minor procedure was colonoscopy/oesophago-gastroduodenoscopy (51 minutes duration) and the patient was given 5 infusions for a total simoctocog alfa dose of 252.55 IU/kg with an overall efficacy rating of excellent and no bleeding being expected or observed. The major procedure was revision of right total knee (150 minutes duration) and the patient was given 15 infusions for a total simoctocog alfa dose of 746.88 IU/kg and there was no difference between the actual and expected blood loss. The dosages administered for the surgeries in the 2 patients in the SURG population are summarised below in Table 18.

Table 18: GENA-01 - Summary of simoctocog alfa dosages administered for surgeries: SURG population (n=2).

Parameter	Mean	SD	Median	Range
Total dose (IU)	42,750	25,102	42,750	25,000-60,500
Total dose (IU/kg)	499.72	349.59	499.72	252.5-746.9
Pre-operative loading dose (IU/kg)	53.03	3.57	53.03	50.5-55.6
Infusions after end of surgery (IU/kg)	446.69	346.01	446.69	202.0-691.4

6.2.1.15. Concomitant treatments during the study

The majority of patients (78%; 25/32) received at least one concomitant medication during the study. The most frequently used medications (except for surgery) were analgesics in 14 patients and topical products for joint and muscular pain in 8 patients. The most frequently used medications during surgery were analgesics, anaesthetics, psycholeptics and blood products and electrolyte perfusion solutions. No patient received any blood transfusions or any blood cell concentrates during the study.

Five patients did not start any additional medication while receiving simoctocog alfa, but continued to take medication received prior to treatment start. These medications included treatments for hypertension, diabetes, acid-related disorders, joint disorders, pain, topical products for muscle and joint disorders, allergens, and chronic obstructive airways disease.

6.2.2. GENA-08 (Phase III) - PTPs adults aged 18 to 75 years

6.2.2.1. Study design, objectives, locations and dates

GENA-08 was designed as a prospective, open-label, single-arm, multinational, multicentre, Phase III study in previously treated patients with severe haemophilia A (FVIII:C ≤ 1%). The study was conducted in 10 investigational centres in Austria (1 centre), Bulgaria (1 centre), Germany (3 centres) and the UK (5 centres), between 22 June 2010 and 31 January 2012. The CSR was dated 19 July 2012. The Co-ordinating Investigator was located at the Experimental Haematology and Transfusion Medicine, Bonn, Germany. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and ICH-GCP (Note for

Guidance CPMP/ICH/135/95), and national regulatory requirements. The study was sponsored by Octapharma, Switzerland.

The **primary objective** of the study was to determine the efficacy of simoctocog alfa during prophylactic treatment, for the treatment of bleeding episodes (BEs), and for surgical prophylaxis, in PTPs with severe haemophilia A.

The **secondary objectives** of the study were: to calculate the incremental recovery of FVIII:C for simoctocog alfa; to investigate the immunogenic potential of simoctocog alfa; and to assess the safety of simoctocog alfa.

The **study planned to enrol** 32 patients. After the first IVR assessment, patients entered the open treatment phase of the study and received simoctocog alfa for routine prophylaxis, breakthrough BEs while on prophylaxis, and surgical prophylaxis. Treatment continued to 6 months and at least 50 EDs. Two additional IVR assessments were scheduled at 3 months and 6 months. The IVR assessment schedule and results have been presented in the *Pharmacokinetics* section of this CER.

During the screening visit, inclusion and exclusion criteria were checked, informed consent was obtained, and demographic data and patient baseline characteristics, as well as results of a general physical examination including the assessment of the HJHS, were recorded. In addition, patients were instructed on how to document treatment details, haemostatic efficacy assessments, adverse events (AEs) and concomitant medication in the patient diary provided.

All patients who completed Visit 1 received sufficient quantities of simoctocog alfa for home treatment. At Visit 2, which was to take place not less than 48 hours after the first infusion, the first prophylactic infusion of simoctocog alfa was administered and a blood sample for inhibitor and antibody testing was obtained prior to the infusion. Subsequently, patients continued prophylactic and on-demand treatment (in case of breakthrough bleeds) with simoctocog alfa.

Follow-up visits were scheduled after 10 to 15 EDs and at 3 months (±2 weeks) and 6 months (+2 weeks). At every study visit, diaries were reviewed and patients were tested for FVIII inhibitors and antibodies. These visits were to be preceded by a FVIII wash-out phase of at least 48 hours. Additionally, at 3 and 6 months, safety laboratory tests were performed and vital signs measured. The study completion visit at 6 months also included a physical examination after the last blood sample had been taken. Treatment parameters recorded for prophylactic infusions and for the on-demand treatment of BEs were presented. For patients undergoing surgical interventions, treatment details were documented for the pre-, intra-, and postoperative phase.

In cases where inhibitor development was suspected additional FVIII inhibitor and anti-rFVIII antibody tests were to be performed. Other reasons for unscheduled visits were the occurrence of serious adverse events (SAEs) or hospitalisations because of severe BEs or because of a surgical intervention. AEs and use of concomitant medication were documented throughout the study. The patients' diaries, including any BEs, treatment of BEs, concomitant medications and AEs, were reviewed and data transferred to the CRF.

Efficacy and safety data (including inhibitor data) were reviewed by an IDMC, which convened after the last patient, had completed the study. The IDMC reviewed the safety and efficacy data and in particular adjudicated on the personal efficacy assessments for the treatment of BE. The IDMC was informed at regular intervals about the progress of the study and the entire clinical development program for simoctocog alfa. The IDMC was composed of recognised experts in the field of haemophilia clinical care who were not actively recruiting patients, and an experienced biostatistician.

6.2.2.2. Inclusion and exclusion criteria

The inclusion and exclusion criteria for GENA-08 were consistent with those previously described for GENA-01. However, no upper age limit was specified for patients in GENA-08 (c.f.,

≤ 65 years for GENA-01). The study also included standard criteria relating to withdrawal from therapy or assessment with adequate procedures for follow-up.

6.2.2.3. Treatment

Simoctocog alfa was administered to all patients prophylactically, for treatment of BEs occurring while on prophylaxis and (where needed) for surgical prophylaxis. A dose of 50 IU/kg was administered at Visit 1 and at 3 and 6 months for the purpose of assessing IVR. Simoctocog alfa was administered as an iv bolus injection at a maximum speed of 4 mL/minute.

6.2.2.3.1. Prophylactic treatment

Patients being treated prophylactically were to receive 30 to 40 IU FVIII/kg every other day until 6 months and at least 50 EDs had been reached. Two dose escalations of +5 IU/kg each were allowed in case of an inadequate response defined as ≥ 2 spontaneous BEs during one month. Any bleeding occurring during the prophylactic treatment period was treated in accordance with the on-demand treatment guidelines.

6.2.2.3.2. On-demand treatment

The procedures to be followed for BEs were identical to those described for GENA-01.

6.2.2.3.3. Surgical prophylaxis

The procedures to be followed for surgical prophylaxis were identical to those described for GENA-01.

6.2.2.3.4. Prior and concomitant treatment

The procedures to be followed for prior and concomitant treatment were identical to those described for GENA-01.

6.2.2.4. Efficacy variables and outcomes

6.2.2.4.1. Prophylactic treatment

The frequency of spontaneous breakthrough bleeds/months under prophylactic treatment was assessed as excellent, good, moderate or poor using the following criteria:

- ***Excellent*****:** Less than 0.75 spontaneous BEs per month.
- ***Good*****:** Between 0.75 and 1 spontaneous BE per month.
- ***Moderate:*** Between 1 and 1.5 spontaneous BEs per month.
- ***Poor*****:** More than 1.5 spontaneous BEs per month.

This overall efficacy assessment of prophylactic treatment per patient was undertaken after a total of 50 EDs and at the end of the study.

In addition to the primary analysis of spontaneous BEs, an assessment of the monthly bleeding rate for all types of bleedings was performed.

The following parameters were also documented: dates and times of study product infusions; details of dose(s) and batch numbers used for prophylactic treatment (in IU); and details of BEs (if any) occurring under prophylactic treatment.

Study product consumption data (FVIII IU/kg per month, per year) per patient and in total were also evaluated.

6.2.2.4.2. Bleeding episodes

At the end of a BE, an efficacy assessment was made using the same categories as defined for GENA-01 (that is, excellent, good, moderate, and none). In addition, the details of all BEs occurring during the study period were documented and these were the same as those

described for GENA-01. In GENA-08, at the end of a BE patients were to return to their regular simoctocog alfa prophylactic treatment regimen.

6.2.2.4.3. Surgical prophylaxis

The procedures and efficacy assessments to be followed for surgical prophylaxis were consistent with those described for GENA-01. In GENA-08, at the end of surgical prophylaxis patients were to return to their regular simoctocog alfa prophylactic regimen.

6.2.2.5. Primary efficacy outcome

The primary endpoint was the efficacy of simoctocog alfa for prophylaxis, for treatment of BEs and for surgical prophylaxis.

- For prophylactic treatment, the primary efficacy variables were the overall efficacy assessment after a total of at least 50 EDs at the end of the study and consumption of simoctocog alfa (FVIII IU/kg per month, per year) per patient and in total.
- For on-demand treatment of BEs, the primary efficacy variable was the efficacy assessment at the end of the BE.
- For surgical procedures, primary efficacy variables were the overall efficacy assessment after the end of the surgical prophylactic treatment phase, and average and maximum expected estimated blood loss compared with actual estimated blood loss.

6.2.2.6. Randomisation and blinding methods

Not applicable as the study was open-label and treatment was single-arm.

6.2.2.7. Analysis populations

Efficacy analyses undertaken in the ITT population were specified to be the most relevant. Efficacy analyses were also undertaken in the PP population to evaluate the robustness of the primary analysis in the ITT population. Three basic populations were used for analysis:

- ***SAF***: All patients who received at least one dose of simoctocog alfa.
- ***ITT analysis population***: All patients in the SAF for whom any data were collected post-treatment with simoctocog alfa. Sub-populations of the ITT population were patients with breakthrough bleeding, and patients with surgical interventions.
- ***Efficacy PP analysis population***: All patients in the ITT analysis population who completed the study without significantly violating the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the efficacy results. Objective criteria for exclusion from the PP population were defined prior to database lock.

In addition to the basic populations, the following study populations were defined:

- *Population of subjects on prophylactic treatment schedule (PROPH and PROPH-PP)*: All patients in the ITT population (PROPH) or the PP populations (PROPH-PP) who received at least one prophylactic infusion.
- *Population of BEs (BLEED and BLEED-PP):* All documented BEs in patients in the ITT population (BLEED) or PP population (BLEED-PP) for which any amount of treatment with simoctocog alfa was documented.
- *Surgery population (SURG and SURG-PP):* All documented surgical interventions of patients in the ITT population (SURG) or the PP population (SURG-PP) for which any amount of simoctocog alfa prior to, during or after the surgery was documented and no other FVIII concentrate was documented within 24 hours prior to surgery.
- *Infusions analysis population (Safety-INF):* All documented infusions with simoctocog alfa to patients of the SAF population

6.2.2.8. Sample size

No formal sample size estimation was performed.

6.2.2.9. Statistical methods

The statistical analysis of all endpoints was exploratory, and no confirmative statistical analysis was planned.

Due to the limited number of patients, no stratification for any subgroup analyses was planned, except for subgroups of patients with BEs and those with surgeries, and subgroup analyses of IVR for age groups 12 to less than 18 years and 18 years or older if there were at least 5 evaluable patients in each age group. No subgroup analyses of the IVR based on age were carried out as there were no patients aged 12 to less than 18 years.

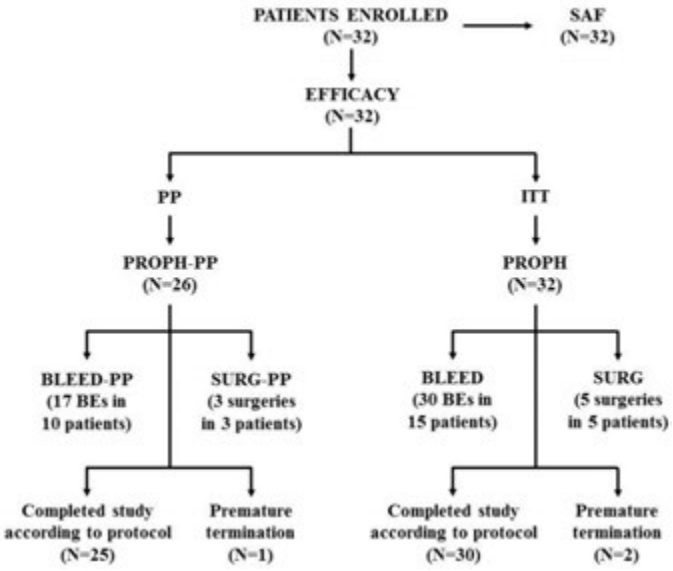
In case of a sufficient number of patients (BEs or surgeries per centre) a descriptive examination of the primary efficacy endpoint for centre effects was planned. However, as only 2 of the centres recruited 5 or more patients no treatment-by-centre efficacy outcome assessments were undertaken.

In general, missing values were not replaced. In the case of missing body weight, the last available weight measurement was used for calculation of recovery (last observation carried forward). No interim analyses were planned or carried out. The data were presented to the IDMC at the end of the study before database close. The IDMC reviewed the safety and efficacy data and in particular adjudicated on the personal efficacy assessments of the treatment of BEs.

6.2.2.10. Participant flow

A total of 32 patients were enrolled and included in both the SAF and ITT populations (see Figure 6 below for disposition).

Figure 6: GENA-08 - Patient disposition.



BE = bleeding episode; BLEED = study population of BEs treated with simoctocog alfa; PROPH = study population of patients receiving prophylaxis; ITT = intention-to-treat; PP = per-protocol; SAF = study population of patients in safety analysis; SURG = study population of surgeries treated with simoctocog alfa.

All 32 patients received routine prophylactic treatment with simoctocog alfa and were included in the ITT population (PROPH), and 26 of these patients were included in the PROPH-PP population. Six (6) patients met pre-defined criteria for exclusion from the PP population and were only included in the SAF and ITT populations (5 patients had a time window of ≥ 5 days between two prophylactic doses and 1 patient had less than 50 EDs).

Thirty (30) breakthrough BEs were treated with simoctocog alfa (BLEED population) in 15 patients in the PROPH population, and 17 of these BEs (in 10 patients) were included in the BLEED-PP population.

Surgical procedures where at least one dose of simoctocog alfa was administered were performed on five occasions in 5 patients. Three (3) of these patients were in the PP population and the 3 respective surgical procedures were therefore included in both the SURG and the SURG-PP populations.

Two (2) patients terminated the study prematurely, one (1) in the PROPH-PP and PROPH populations died after 76 documented EDs from an epileptic seizure on Day 202 deemed unrelated to study treatment, and one (1) in the PROPH population withdrew consent after 17 EDs.

6.2.2.11. Major protocol deviations

Thirty-one (31) patients had a least one minor protocol deviation, and major protocol deviations were recorded in 5 patients (none of whom were included in the PROPH-PP population). All 5 patients with major protocol deviations had a time window of ≥ 5 days between prophylactic doses on at least one occasion. In addition, one patient received a monthly prophylactic dose of 208.4 IU/kg (which was less than 80% of the allowed minimum dose of 360.0 IU/kg) as he had received a prophylactic dose of only 20 IU/kg (as opposed to the 30–40 IU/kg stipulated in the protocol) for the first 3.5 months of the study.

6.2.2.12. Baseline data

The basic demographic data of the 32 patients in the ITT/SAF population are summarised below in Table 19.

Table 19: GENA-01 - Demographic characteristics of the study population (ITT/SAF); n=32.

Parameter	Mean	SD	Median	Range
Age at first treatment (years)*	37.3	13.6	35.0	18–75
Height (cm)	178.4	7.9	180.0	158–192
Weight (kg)	82.5	18.0	84.5	47–127
HJHS (Gait)	1.6	1.4	2.0	0–4
HJHS (Total)	34.6	32.2	20.5	0–117

HJHS = Haemophilia Joint Health Score; ins = insertion; ITT = intention-to-treat; SAF = study population of patients in safety analysis.

The majority of patients (29/32; 90.6%) were "White". Known FVIII gene defects were documented for 40.6% (13/32), and most were single occurrence, except for intron 22 inversion, which was observed in 3 patients (9.4%), and small deletions or insertions, which were reported in 2 patients (6.3%). A family history of haemophilia was documented in more than half of the patients (18; 56.3%), and one patient (3.1%) had a family history of inhibitor activity.

FVIII inhibitor levels were less than 0.6 BU in 31 patients at screening. One (1) patient had a relatively high FVIII:C of 0.649 IU/mL as measured by the OS assay at screening, probably due to an infusion of regular FVIII 1 to 2 days before testing. The patient had inhibitor titres of less than 0.6 BU in all further measurements.

The main historical bleeding sites were the ankle (59.4% [19/32] of patients both sides, 15.6% [5/32] and 3.1% [1/32] left and right ankle, respectively), the elbow (40.6% of patients both sides [13/42], 12.5% [4/32] and 21.9% [7/32] left and right elbow, respectively) and the knee

(31.3% [10/32] of patients both sides, 25.0% [8/32] and 18.8% [6/32] left and right knee, respectively).

Of the 32 patients in the ITT/SAF population, 24 (75.0%) had received previous FVIII concentrates within 183 days (6 months) of the start of the study, while data were missing for the remaining 8 patients. Of the 24 patients with data, 22 had received rFVIII concentrates and 2 had received pdFVIII concentrates.

6.2.2.13. Efficacy outcomes - prophylactic treatment during the study

All 32 patients received prophylactic treatment with simoctocog alfa and were included in the PROPH population. The mean±SD number of EDs was 85.1±15.4, the mean±SD duration of prophylactic treatment was 6.0±0.9 months, and the mean±SD dose per infusion was 32.8±2.8 IU/kg. The total number of prophylactic injections was 2722 and 2519 of these injections were administered 2 days after the last simoctocog alfa infusion as per-protocol. This corresponds to 2519 (93.6%) out of 2690 prophylactic infusions in 32 patients (that is, total number of prophylactic infusions minus the first prophylactic infusion). The number of EDs and dosage of simoctocog alfa administered as prophylaxis in this population are summarised below in Table 20.

Table 20: GENA-08 - EDs and dosage for prophylactic treatment with simoctocog alfa (simoctocog alfa/Human-cl rhFVIII); PROPH population, n=32.

Parameter	Mean	SD	Median	Range
Number of EDs	85.1	15.4	89.0	16–100
Number of infusions per ED	1.0	0.0	1.0	1–1
Duration of prophylactic treatment (months)	6.0	0.9	6.1	1.3–7.3
Total dose of Human-cl rhFVIII (IU)	226,596	59,767	228,020	56,000–325,548
Average amount of Human-cl rhFVIII per month of study (IU/kg/month)	466.1	65.5	468.7	208.4–582.6
Average dose of Human-cl rhFVIII per infusion (IU)	2689	572	2503	1500–4063
Average dose of Human-cl rhFVIII per infusion (IU/kg)	32.8	2.8	33.1	24.0–39.3

ED = exposure day; IU = international unit; PROPH = study population of patients receiving prophylaxis; SD = standard deviation.

A total of 44 BEs occurred during the study (that is, between Visit 1 and the completion visit), 30 of which required treatment with simoctocog alfa. Of the 44 BEs, 28 (63.6%) were minor bleeds, 16 (36.4%) were moderate to major bleeds, and there were no major to life-threatening bleeds. Twenty-six bleeds (59.1%) were spontaneous, 16 (36.4%) were traumatic bleeds, and 2 (4.5%) were bleeds due to other causes.

Of the 32 patients in the prophylactic population (PROPH population), no BEs were reported in 16 patients (50%), 1 BE in 11 patients (34.4%), 5 BEs in 1 patient (3.1%), 6 BEs in 1 patient (3.1%), 7 BEs in 2 patients (6.3%), and 8 BEs in 1 patient (3.1%). The mean total number of BEs (44 BEs) during the study was 1.4±2.4 per patient (median 0.5; range 0, 8). When excluding BEs occurring under surgical prophylaxis and BEs occurring between the first dose for IVR assessment and the start of prophylactic treatment, the mean number of BEs per patient during the study was 0.6±1.2 for spontaneous BEs (median 0; range 0, 4) and 1.1±1.8 for all types of BEs (median 0.5; range 0, 7). The corresponding mean monthly bleeding rates per patient during the prophylactic treatment period at the end of the study were 0.095±0.211 for spontaneous bleeds (median 0; range 0, 0.71), and 0.188±0.307 (median 0.074; range 0, 1.21)

for all types of bleeds. There were 16 patients who had a total HJHS of more than 10 in at least one of their joints. Of these, only 3 patients experienced bleeds in one of their target joints during the study; one patient had one spontaneous and one traumatic bleed in the same target joint and 2 had one traumatic bleed each in one target joint.

The efficacy results for prophylactic treatment with simoctocog alfa as regards both spontaneous and all BEs are summarised below in Table 21. Efficacy was classed as excellent (that is, BEs < 0.75 / month) for 90.6% (29/32) of patients as regards all BEs occurring while on simoctocog alfa, and for 100% (32/32) of patients as regards spontaneous BEs.

Table 21: GENA-08 - Overall assessment of prophylactic treatment at the end of the study; PROPH population, n=32.

	Excellent (<0.75)	Good (0.75 - 1.0)	Moderate (>1.0 - 1.5)	Poor (> 1.5)
Spontaneous BEs	32 (100.0%)	-	-	-
All types of BEs	29 (90.6%)	2 (6.3%)	1 (3.2%)	-

BE = bleeding episode; PROPH = study population of patients receiving prophylaxis.

6.2.2.14. Prophylactic treatment historical (pre-study) vs study

The study also included a comparison between historical (pre-study) prophylaxis and routine simoctocog alfa prophylaxis (study) for dose and monthly BE rate in patients in the prophylactic (PROPH) population. The results (mean±SD) for the historical (pre-study) and on-study (study) doses and BEs are summarised below in Table 22.

Table 22: GENA-08 - Historical (pre-study) and on-study (study) data (mean±SD) for monthly BE rate and prophylactic dosage in patients in the study categorised by patients who received previous prophylaxis, patients who received previous on-demand treatment and all patients combined; PROPH population, n=32.

Patient group		PROPH dose (IU/kg/month)		BEs/month	
	N	Historical	Study	Historical	Study
Previous prophylaxis, patients	21	292.6± 117.1	451.2 ±73.4	0.540±0.927	0.263±0.354
Previous on-demand, patients	11	-	494.6 ±33.7	3.924±2.845	0.043±0.074
All patients	32	292.6± 117.1 *	466.1 ±65.5	1.703±2.4152	0.188±0.307

* Only patients who had received prophylaxis prior to the study were considered for this calculation. BE = bleeding episode; IU = international unit; PROPH = study population of patients receiving prophylaxis.

The results for the comparison between the historical outcomes (pre-study) and the study outcomes in the patients (n=21) who received previous prophylactic treatment with FVIII concentrated and prophylactic study treatment with simoctocog alfa showed that the mean dose was about 54% higher during the study compared with pre-study (451.2±73.4 vs 292.6±117.1 IU/kg/month, respectively), while the mean BE rate was about 50% lower during the study compared with pre-study (0.263 vs 0.540 BEs/month, respectively). In almost all patients who had received previous prophylactic treatment (81%, 17/21), the monthly rate of BEs decreased or remained constant during the study. One (1) of the 4 patients in whom monthly BE rates increased showed a marginal increase from 0.167 BEs/month pre-study to 0.168 BEs/month at study end, and one 1 patient received a 15% lower monthly FVIII dose during the study compared with previous treatment. In 1 patient with a previously very low frequency of BEs, the frequency at the end of the study was approximately 10-fold higher (0.847 vs 0.083) because the patient experienced 5 BEs during the study (4 traumatic and 1 spontaneous). In all 11 patients who had received on-demand treatment prior to the study, mean ±SD monthly BE rates were markedly reduced while on prophylactic treatment during the study (3.924±2.845 pre-study falling to 0.043±0.074 during the study). Of the 11 patients who had received previous on-demand treatment, 8 experienced no BEs at all during the study while on simoctocog alfa prophylactic treatment and the remaining 3 patients had low monthly BE rates of 0.148 to 0.166.

6.2.2.15. Efficacy outcomes - treatment of breakthrough bleeding episodes during the study

Out of the 44 BEs occurring during the study, 30 BEs were treated with at least one dose of simoctocog alfa. These 30 BEs occurred in 15 patients and constitute the BLEED population. The remaining 14 BEs were not treated with either simoctocog alfa or with any other FVIII concentrate. These 14 BEs were all minor and occurred in only 4 patients, who experienced 1, 2, 4 and 7 untreated BEs.

Of the 30 treated BEs, 14 were spontaneous, another 14 were due to trauma, and the remaining 2 were classified as "other". The most frequent sites of bleeding were the ankle and the knee, which together accounted for 60% of all BEs. Other affected sites were the elbow, the leg, the arm, the oral cavity and other sites (including shoulder, finger, toe, chest soft tissue and a traumatic head bleed). Across all sites, 14 treated BEs (46.7%) were rated as minor and 16 as moderate to major (53.3%). There were no major to life-threatening BEs. A total of 49 infusions were administered for the treatment of BEs. The EDs and the simoctocog alfa dosages for treatment of BEs are summarised below in Table 23.

Table 23: GENA-08 - Treatment summary of breakthrough BEs in the BLEED population (30 BEs in 15 patients).

Parameter	Mean	SD	Median	Range
Number of EDs (for bleedings)*	1.60	1.55	1.00	1–8
Dose of Human-cl rhFVIII per BE, IU	5037.0	5824.2	4000.0	1500–24,000
Dose of Human-cl rhFVIII per BE, IU/kg	60.4	73.4	33.3	20–353
Number of dosages administered*	1.80	2.37	1.00	1–12
Dose of Human-cl rhFVIII per infusion, IU	2775.5	872.4	2500.0	1500–4000
Dose of Human-cl rhFVIII per infusion, IU/kg	33.3	6.7	32.1	20–53

* Dosage used to treat several simultaneous bleedings is counted only once.

The median number of infusions across all BEs was 1, and the mean number was 1.8 (range: 1, 12). The difference between mean and median values is mainly due to 3 BEs that were treated with a relatively high number of infusions (6, 5 and 12, respectively) over several EDs (3, 5 and 8 EDs, respectively).

On three occasions, 2 simultaneous BEs were reported in one patient, which were counted as separate BEs, but treated with the same infusion. Therefore, there were 27 occasions of BE treatment. On 88.9% of occasions, 1 (81.5%) or 2 (7.4%) infusions were sufficient to treat the BE, while on one occasion (3.7%) each, 5, 6 and 12 infusions were administered, respectively. The BE requiring 12 infusions was a moderate to major BE at the ankle caused by a trauma, and treatment of this BE also required the maximum number of EDs and the maximum dose of simoctocog alfa (both total and per kg). The median dose of simoctocog alfa per infusion was 32.1 IU/kg across all BEs (range: 20, 53), and was 32.1 IU/kg for minor BEs and 31.5 IU/kg for moderate to major BEs.

Personal efficacy assessments were available for 28 BEs (14 minor; 14 moderate-major). Personal efficacy ratings on the four-point scale were excellent or good for all 28 BEs (20 [71.4%] excellent; 8 [28.6%] good), for all 14 minor BEs (12 [85.7%] excellent; 2 [14.3%] good), and for all 14 major BEs (8 [57.1%] excellent; 6 [42.9%] good). No personal efficacy assessments were available for the remaining 2 BEs.

At the end of the study, the IDMC adjudicated on all personal efficacy assessments, primarily considering the number of infusions administered for each BE. In 6 cases, the IDMC assessment differed from the personal assessment. In 3 cases in which the personal assessment had been "good", efficacy was judged "moderate"; in 2 cases in which the personal assessment had been "good", efficacy was rated "excellent"; and in 1 case where no personal assessment was available, efficacy was rated "excellent" by the IDMC.

6.2.2.16. Efficacy outcomes - surgery

During the study, 6 patients underwent 6 surgical procedures, 5 of which were major. In 1 of the 6 patients, surgery was an emergency total knee replacement following an accident treated with a different FVIII concentrate and therefore not included in the analysis. Consequently, the surgery (SURG) population (treated with simoctocog alfa) included 5 patients (4 major surgeries, 1 minor surgery). The mean duration of surgery was 79.0±63.4 minutes, ranging from 5 to 170 minutes. The mean expected duration was 62.0±43.1 minutes, with deviations from the respective estimated durations ranging between –55 minutes for a cholecystectomy and liver biopsy and +125 minutes for a total hip replacement. The 5 surgeries in the 5 patients are summarised below in Table 24.

Table 24: GENA-08 - Surgical procedures; SURG population, 5 surgeries in 5 patients.

Type of surgery	Description of surgery	Difference between actual and expected average blood loss (mL)	Number of infusions	Total dose (IU/kg)	Overall efficacy rating
Major	Joint arthroscopy	50	25	1028.74	Moderate
Major	Bilateral ankle joint arthroscopic debridements	–20	9	320.92	Excellent
Major	Total hip replacement	–500	16	480.39	Excellent
Major	Cholecystectomy and liver biopsy	N/A	5	183.33	Excellent
Minor	Tooth extraction	N/A	3	95.45	Excellent

IU=international unit; N/A=no data available; SURG=study population of surgeries treated with simoctocog alfa

The minor surgery required 3 infusions over 3 EDs, and the 4 major surgeries required 5, 9, 16 and 25 infusions over 3, 5, 8 and 18 EDs, respectively. A loading dose prior to surgery was administered for all surgical procedures; 4 patients received 1 infusion, and 1 patient received 2 infusions of 4000 and 1000 IU, respectively. The second infusion of 1000 IU was administered because the local laboratory measured a FVIII plasma concentration of 0.96 IU/mL (96%) after the first infusion of 4000 IU and, as per local policy, the FVIII level was to be at least 1.0 IU/mL (100%) pre-surgery. No maintenance doses during surgery were required for any patient. Simoctocog alfa dosage administered to the SURG population is summarised below in Table 25.

Table 25: GENA-08 - Dosages for surgical procedures; SURG population, 5 surgeries in 5 patients.

Parameter	Mean	SD	Median	Range
Total dose of Human-cl rhFVIII (IU)	37,680.0	32,711.4	25,000.0	8400–89,500
Total dose of Human-cl rhFVIII (IU/kg)	421.77	369.24	320.92	95.5–1028.7
Pre-operative loading dose (IU/kg)	49.61	6.58	50.00	39.2–57.5
Infusions after end of surgery (IU/kg)	372.16	366.74	269.58	45.5–971.3
Total dose of Human-cl rhFVIII per ED (IU/kg)	54.86	13.13	60.05	31.8–64.2
Dose of Human-cl rhFVIII per infusion (IU)	3104.06	341.16	3062.50	2777.8–3580.0
Dose of Human-cl rhFVIII per infusion (IU/kg)	35.06	4.36	35.66	30.0–41.1

ED = exposure day; IU = international unit; SD = standard deviation; SURG = study population of surgeries treated with simoctocog alfa.

The lowest total dose of simoctocog alfa was required for the minor surgery, and mean doses per ED were approximately twice as high for the major surgeries compared with the minor surgery (60.6 vs 31.8 IU/kg/ED), while doses per kg and infusion were comparable between the surgery groups. For 3 surgeries, average and maximum expected and actual blood loss were reported. For 2 procedures with an expected average blood loss of 20 mL and 500 mL, no actual blood loss was observed, while for one surgery the actual blood loss was 100 mL, which was 50 mL higher than the average expected blood loss but still markedly below the expected maximum blood loss of 600 mL.

For 4 surgeries (1 minor and 3 major), efficacy was rated as excellent intra-operatively and overall. For one major surgery ([information redacted]/joint arthroscopy/bilateral ankle) intra-operative efficacy was rated as good and overall efficacy as moderate. This patient experienced a total of 7 BEs during the study, but all of them were minor nose or oral cavity bleeds that did not require treatment.

6.2.3. GENA-03 (Phase III study) - children aged 2 to 12 years

6.2.3.1. Study design, objectives, locations, and dates

GENA-03 was designed as a prospective, non-controlled, open label, multinational, multicentre, Phase III study in previously treated paediatric patients with severe haemophilia A (FVIII:C <1%) and at least 50 previous EDs to FVIII concentrates. The enrolled patient population (n=59) was aged 2-12 years, and results were assessed in the total population and in two subgroups (29 aged 2–5 years; 30 aged 6–12 years). The study was designed to enrol 60 patients, but 59 were actually enrolled.

The study was conducted at 15 sites in 7 countries (UK [2 sites], Czech Republic [1 site], Poland [3 sites], Russia [1 site], Turkey [5 sites], France [2 sites], Romania [1 site]). The study was conducted from 27 December 2010 through to 6 November 2012, and the final CSR was dated 15 February 2013. The principal/co-ordinating investigator was located at the Great Ormond Street Hospital for Children, London, England. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and ICH-GCP (Note for Guidance CPMP/ICH/135/95), and national regulatory requirements. The study was sponsored by Octapharma, Switzerland.

The **primary objective** was to assess the clinical efficacy of simoctocog alfa in terms of prevention (prophylactic treatment) and treatment of (breakthrough) BEs in previously treated children suffering from severe haemophilia A (FVIII:C <1%).

The **secondary objectives** were: to determine the PK parameters and incremental recovery of simoctocog alfa; to investigate the immunogenic potential of simoctocog alfa by assessing the inhibitor titre; to assess clinical efficacy of simoctocog alfa in surgeries; and to assess safety of simoctocog alfa in terms of adverse event (AE) monitoring.

The study included two phases: **Phase I (PK) and Phase II (efficacy and incremental recovery).** The results for Phase I have been reviewed in the *Pharmacokinetics* section of this CER. Twenty-seven (27) patients participated in the PK phase (Phase I) of the study. The 27 patients who completed Phase I plus 32 additional patients (16 in each age group) were followed up for a period of at least 6 months and at least 50 EDs (Phase II). During this phase, prophylactic and on-demand treatments (in case of breakthrough bleeds) with simoctocog alfa were documented. In patients who underwent surgical interventions, treatment details were documented for the pre-, intra-, and post- operative phase, respectively.

During the screening visit, inclusion and exclusion criteria were checked, informed consent was obtained, and demographic data and baseline characteristics were recorded. For the patients undergoing PK analysis, Cycle 1 was to take place no later than 4 weeks after the screening visit. For patients not participating in Phase I, incremental recovery assessments undertaken in Phase II were to start no later than 4 weeks after the screening visit. It was intended that all patients were to continue prophylactic treatment (and on-demand treatment in case of breakthrough BEs) with simoctocog alfa after completion of either Phase I PK assessment or Phase II recovery assessment. Parents/guardians were to receive sufficient quantities of simoctocog alfa for home treatment, as well as detailed instructions on how to administer the product and record outcomes.

Follow-up visits were scheduled after 10 to 15 EDs (Interim Visit 1), at 3 months (±2 weeks), after 50 EDs (Interim Visit 2) and at 6 months (+2 weeks). Interim visits were preceded by a FVIII wash-out of at least 48 hours and 3-month and 6-month visits by a 72-hour wash-out. Additionally, at 3 and 6 months, safety laboratory tests were performed and vital signs were measured. Patient diaries were reviewed at each study visit. The study completion visit at 6 months was also to include a physical examination and HJHS after the last blood sample had been taken. In addition, monthly compliance checks were to take place either by telephone or by a personal visit on the part of the patient in order to check whether the patient followed the every-other-day or 3-times-weekly treatment regimen and whether the given dose was adequate.

In cases where inhibitor development was suspected additional FVIII inhibitor and anti-rhFVIII antibody tests were to be performed. Other reasons for unscheduled visits included the occurrence of serious adverse events (SAEs) or hospitalisations because of severe BEs or surgical interventions. AEs and use of concomitant medication were documented throughout the study. Patient diaries, including any BEs, treatment of BEs, concomitant medications and AEs, were reviewed and data transferred to the CRF.

6.2.3.2. Inclusion and exclusion criteria

The **inclusion criteria** were:

1. Severe haemophilia A (FVIII:C <1%).
2. Age ≥2 and 12 years.
3. Previously treated with FVIII concentrate, at least 50 EDs;
4. Immunocompetence (CD4+ count >200/µL);
5. Human immunodeficiency virus (HIV) negative or if positive, respective viral load <200 particles/µL or <400,000 copies/mL.
6. Freely given written informed consent by parents or legal guardian and by patients (depending on their developmental stage and intellectual capacity).

The exclusion criteria were consistent with those for GENA-01 and GENA-08. The study also included standard criteria for withdrawal from the study.

6.2.3.3. Treatments

- **Prophylactic treatment**

For prophylactic treatment in Phase II, 30–40 IU FVIII/kg BW of simoctocog alfa were administered every other day or 3-times-weekly for a period of at least 6 months and at least 50 EDs. The protocol initially specified every-other-day dosing, but this was subsequently amended to allow 3-times-weekly dosing when it was realised that patients were reluctant to enter the study because of the requirement for every other day dosing. Two dose escalations of +5 IU/kg BW each were allowed in case of an inadequate response defined as ≥2 spontaneous BEs within one month. Any BE that occurred during the prophylactic treatment period was treated in accordance with the on-demand treatment guideline.

- **On-demand treatment**

The on-demand treatment regimen for breakthrough BEs was the same as that used for on-demand treatment of BEs in GENA-01 and on-demand treatment for breakthrough BEs in GENA-08.

- **Surgical prophylaxis**

The surgical prophylaxis regimen was the same as that used in GENA-01 and GENA-08.

- **Prior and concomitant treatment**

The procedures to be followed for prior and concomitant treatments were identical to those for GENA-01 and GENA-08.

6.2.3.4. Efficacy variables and outcomes

6.2.3.4.1. Prophylactic treatment

The parameters to be documented and the efficacy criteria for assessment of prophylactic treatment were identical to those used in GENA-08.

The time periods for prophylactic treatment were: the time between first prophylactic treatment with simoctocog alfa until the administration of the 50th ED; and the time between first prophylactic treatment with simoctocog alfa until the administration of the last prophylactic treatment + 2 days or study completion, whichever came first.

The number of BEs counted for prophylactic treatment efficacy assessment comprised all spontaneous BEs starting during the time periods for prophylactic treatment defined above. BEs categorised as traumatic, post-operative or "other" were not included in the primary prophylactic treatment assessment.

6.2.3.4.2. Bleeding episodes

The parameters to be documented and the efficacy for assessment of BEs were identical to those used in GENA-01 and GENA-08. All parameters relating to BEs were documented by the parent/guardian (together with the investigator in case of on-site treatments) in the patient diary. Patients who experienced a major or life-threatening BE should preferably have been treated at the study site. The efficacy assessment was made at the end of a BE. After the end of a BE, patients were to return to their regular prophylactic treatment regimen.

6.2.3.4.3. Surgical prophylaxis

The procedures to be followed for surgical prophylaxis were consistent with those used in GENA-01 and GENA-08 as were all relevant efficacy definitions. The conclusion of the post-operative phase of a major surgery was defined as the date of discharge, or at least post-operative day 6, whichever occurred later. The regular simoctocog alfa prophylactic treatment regimen was to resume at the end of surgical prophylactic treatment.

6.2.3.5. Randomisation and blinding

Not applicable to Phase II (efficacy) as treatment was open-label and single-arm.

6.2.3.6. Analysis populations

All populations for analysis of efficacy and safety were either identical to or consistent with those in GENA-08. The PROPH population was considered to be the most relevant for analysis of efficacy data on prophylaxis, the BLEED population was considered to be the most relevant for analysis of efficacy data on bleedings and the SURG population was considered to be the most relevant for analysis of efficacy data on surgeries. To evaluate the robustness of the study results efficacy analyses were also undertaken in the PP population. The PK-PP population was the primary analysis population for the PK data (Phase I).

6.2.3.7. Sample size

No formal sample size calculation was undertaken. The sample size was chosen to satisfy current CHMP recommendations.

Comment: According to the updated CHMP Guideline on the Clinical Investigation of new FVIII products, a study in children is to be performed in at least 50 patients suffering from severe haemophilia A. Of those 50, at least 25 should be aged between 2 and 5 and at least 25 aged between 6 and 12 years. Therefore, the study planned to include a total of 60 patients (30 aged 2–5 years and 30 aged 6–12 years) in order to meet the CHMP requirements while compensating for discontinuations. The investigation of the PK properties of simoctocog alfa and the previously used FVIII concentrate in up to 13 patients (12 evaluable) of each age cohort was part of the study and is consistent with the updated CHMP recommendations. The number of children included in this study is also consistent with the TGA adopted CHMP Guideline on the Clinical Investigation of new rFVIII products which specifies that at least 20 children under that age of 6 regardless of prior treatment should be included in an open multicentre trial. The adopted guideline also states that the mandatory study in children "may be submitted after a marketing authorisation is granted".

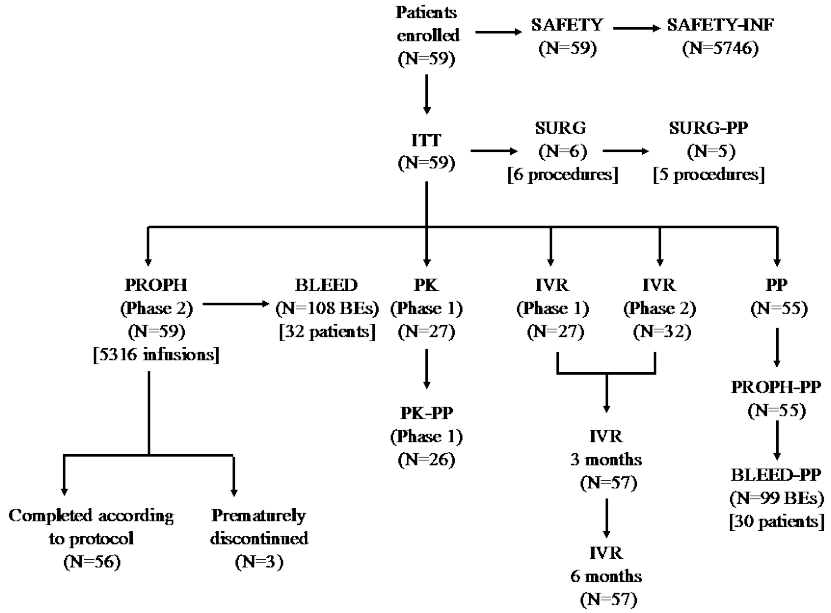
6.2.3.8. Statistical methods

The statistical analyses of all endpoints were exploratory, and no confirmatory statistical analyses were planned.

6.2.3.9. Participant flow

The patient disposition is summarised below in Figure 7.

Figure 7: GENA-03 - Patient disposition.



BLEED = study population of BEs treated with simoctocog alfa; PROPH = study population of patients receiving prophylaxis; ITT = intention-to-treat; IVR = in vivo recovery; PK = pharmacokinetics; PP = per-protocol; SAFETY = study population of patients in safety analysis; SAFETY-INF = all infusions within safety population; SURG = study population of surgeries treated with simoctocog alfa.

There were 59 patients enrolled in the study and 56 completed while 3 prematurely discontinued. All 59 enrolled patients were included in the safety and ITT populations. All 59 enrolled patients received prophylactic treatment with simoctocog alfa (PROPH population) and 55 of these patients were included in the PROPH-PP population. The reasons for 4 exclusions from the PROPH-PP population were: 1 patient with less than 50 EDs with simoctocog alfa; 1 patient with extremely long gap between 2 doses after start of prophylactic treatment; 1 patient with less than 50 EDs with simoctocog alfa, violation of inclusion and exclusion criteria and use of other FVIII product after starting prophylactic treatment with simoctocog alfa; and 1 patient due to use of other FVIII product after starting prophylactic treatment with simoctocog alfa.

Three patients terminated the study prematurely, and all were included in the PROPH population while 2 were also included in the PROPH-PK population. The reasons for the premature discontinuations were: *1 patient* withdrawn due to therapy failure after 71 days in the study and 44 study product administrations and 42 EDs. He experienced a spontaneous moderate to major bleeding in the right ankle that was unsuccessfully treated with simoctocog alfa over 10 EDs (12 infusions), followed by pdFVIII (that is, FVIII presented as a complex with von Willebrand factor). He had previously experienced another 2 BEs (one minor, one moderate to major), for which the treatment was rated as good for one and moderate for the other. His IVR was 2.29% per IU/kg after administration of simoctocog alfa and higher than in PK Cycle 1 after administration of pdFVIII (1.87% per IU/kg). The day he started pdFVIII prophylaxis, he was withdrawn from the study due to insufficient therapeutic response; *1 patient* had his 6-month assessment 3 days earlier than planned after 180 days in the study and after 88 simoctocog alfa administrations. This patient was included in the PK and PROPH population; and *1 patient* was diagnosed with VWD after a surgical procedure during which he did not respond to simoctocog alfa. He was withdrawn 4 days after surgery, after 52 days in the study and after 26 simoctocog alfa administrations during which time no BEs had occurred.

6.2.3.10. Major protocol deviations

Major protocol deviations were reported in 3 (5.1%) of the 59 patients. The major protocol deviations were: use of other FVIII concentrate after start of prophylaxis (2 patients); violation of inclusion criteria (1 patient); violation of exclusion criteria (1 patient); reason for study completion not according to protocol (1 patient); simoctocog alfa treatment before 48 hour sampling for PK assessment (1 patient); and extremely long gap between 2 doses after start of prophylactic treatment (1 patient).

Minor protocol deviations were reported in 57 (96.6%) of the 59 patients. The most commonly reported minor protocol deviations reported in ≥ 10% of patients were: 6-month visit outside the 6 months (+2) weeks window in 28 (47.5%) patients; prophylactic dose not between 25 and 45 IU/kg in 23 (39.0%) patients; wash-out period for recovery assessment not followed in 21 (35.6%) patients; interim visit not between ED 10 and ED 20 in 17 (28.8%) patients; FVIII sampling time outside the window in 11 (18.6%) patients; sample for central laboratory assessment not taken in 7 (11.9%) patients; 3-month visit outside the 3 months (±2 weeks) window in 6 (10.2%) patients; and local laboratory result not reported in 6 (10.2%) patients.

6.2.3.11. Baseline data

All 59 patients enrolled in the study were white males. The mean±SD age was 6.1±2.97 years (median 6.0 years), and all patients were in the protocol specified age range of 2 to 12 years. The mean±SD height was 122.5±19.78 cm, and the mean±SD weight was 26.7±12.33 kg. Known FVIII gene defects were documented for 56 (94.9%) patients. Most gene defects were single occurrence, except for intron 22 inversion and missense mutations, which were observed in 25 (42.4%) and 11 (18.6%) patients, respectively. A family history of haemophilia was documented in 24 (40.7%) patients.

Total HJHS at baseline (0 [best] to 148 [worst]) ranged from 0 to 11 in 53 patients, with a median score of 0. The HJHS scores indicate good joint health, as expected in this paediatric population of PTPs. The main historical bleeding sites in the 59 patients were the ankle (11.9% [n=7] of patients both sides, 11.9% [n=7] and 18.6% [n=11] left and right ankle, respectively, 1.7% [n=1] unknown); the knee (8.5% [n=5] of patients both sides; 10.2% [n=6] and 11.9% [n=7] left and right knee, respectively); and the leg (10.2% [n=6] of patients both sides; 5.1% [n=2] and 3.4% [n=2] left and right leg, respectively; 1.7% [n=1] unknown).

Plasma FVIII:C at baseline was ≥ 0.01 IU/mL in 18 patients as determined by the CHR assay (n=54), and 39 had values ≥ 0.01 IU/mL or above as determined by the OS assay (n=51). The sponsor comments that the elevated plasma FVIII:C findings in these patients are likely to be due to the absence of a pre-defined wash-out period for the screening visit. Baseline values of FVIII:C before the first PK and IVR assessments were more in line with expected values. FVIII inhibitor levels were <0.6 BU in all 59 patients at screening.

In the 6 months prior to the study, 55.9% (n=33) of patients had received rFVIII concentrates, 45.8% (n=27) of patients had received pdFVIII concentrates, 8.5% (n=5) of patients had received both rFVIII and pdFVIII concentrates. Six (6) patients, 3 from 2 centres in Turkey and 3 from one centre in Romania, had previously received on-demand treatment while the remaining 53 patients had received FVIII concentrates as prophylaxis.

Comment: The sponsor will be requested to provide information relating to the FVIII:C levels recorded before the first PK and IVR assessments in the s31 response to questions raised following the first round evaluation of the submission.

See Section 11.1.2.2.

6.2.3.12. Efficacy outcomes - prophylaxis

All 59 patients received prophylactic treatment with simoctocog alfa and were included in the PROPH population. The total number of prophylactic injections was 5316, and only 172

infusions (3.2%) were administered more than 3 days after the previous infusion (that is, 3 days was the maximum gap in protocol specified 3-times-weekly schedule). Eleven (11) patients had increases in prophylaxis dose, but most were only temporary and often due to their starting dose being judged by the investigator as being too low or following BEs. The number of EDs and dosage of simoctocog alfa administered as prophylaxis are summarised below in Table 26.

Table 26: GENA-03 - EDs and dosage for prophylactic treatment with simoctocog alfa (Human-cl rhFVIII); PROPH population. n=59.

Parameter	Mean	SD	Median	Range
Number of EDs	89.8	22.33	87.0	19–149
Number of infusions per ED	1.0	0.02	1.0	1.0–1.1
Duration of prophylactic treatment, months	6.6	1.4	6.3	1.3–9.8
Total dose of *Human-cl rhFVIII*, IU	95,860	57,044	85,000	19,000–360,000
Average amount of *Human-cl rhFVIII* per month of study, IU/kg/month	527.7	112.3	521.9	332.3–888.5
Average dose of *Human-cl rhFVIII* per infusion, IU	1049	486	1000	300–3000
Average dose of *Human-cl rhFVIII* per infusion, IU/kg	38.9	7.2	37.8	26.0–56.7

ED = exposure day; IU = international units; PROPH = study population of patients receiving prophylaxis; SD = standard deviation.

A total of 129 BEs occurred in 39 patients during prophylactic treatment. Of these 129 BEs, 74 (57.4%) were traumatic, 45 (34.9%) were spontaneous and 10 (7.7%) were classified as "other". In the PROPH population, 20 (33.9%) patients did not experience any BEs and 14 patients (23.7%) experienced only one BE during the study. The overall efficacy assessment of prophylactic treatment with simoctocog alfa is shown below in Table 27.

Table 27: GENA-03 - Overall efficacy assessment (monthly BE rate)* of prophylactic treatment at the end of the study; PROPH population, n=59.**

Age group	n	Type of bleed	Excellent n (%)*	Good n (%)*	Moderate n (%)*	Poor n (%)*
All: 2-12 years	59	Spontaneous BEs	56 (94.9)	1 (1.7)	2 (3.4)	-
	59	Traumatic BEs	55 (93.2)	3 (5.1)	-	1 (1.7)
	59	All BEs	49 (83.1)	5 (8.5)	3 (5.1)	2 (3.4)
Age: 2-5 years	29	Spontaneous BEs	28 (96.6)	1 (3.4)	-	-
	29	Traumatic BEs	29 (100.0)	-	-	-

Age group	n	Type of bleed	Excellent n (%)*	Good n (%)*	Moderate n (%)*	Poor n (%)*
	29	All BEs	27 (93.1)	1 (3.4)	1 (3.4)	-
Age: 6-12 years	30	Spontaneous BEs	28 (93.3)	-	2 (6.7)	-
	30	Traumatic BEs	26 (86.7)	3 (10.0)	-	1 (3.3)
	30	All BEs	22 (73.3)	4 (13.3)	2 (6.7)	2 (6.7)

* Excellent = <0.75 BEs/month; Good = 0.75–1.0 BEs/month; Moderate = >1.0–1.5 BEs/month; and Poor = >1.5 BEs/month. ** Includes all BEs between start of prophylactic treatment and last prophylactic treatment + 2 days or completion visit, whichever came first. BEs between start of treatment for surgery and re-start of prophylactic treatment after surgery were excluded. BE = bleeding episode; ED = exposure day; n = number of patients in analysis group; PROPH = study population of patients receiving prophylaxis.

The monthly rates for spontaneous, traumatic and all BEs are summarised below in Table 28. The monthly rates for all, spontaneous, and traumatic BEs at the end of the study were greater in the 6-12 years age group than in the 2-5 years age group. The monthly rates for traumatic BEs were greater than the monthly rates for spontaneous BEs in both age sub-groups.

Table 28: GENA-03 - Monthly rate of BEs * at end of study (EOS) ** during prophylactic treatment; PROPH, n=59.

Para-meter	Spontaneous BEs/month - EOS			Traumatic BEs/month - EOS			All BEs/month - EOS		
	All n=59	2-5 years n=29	6-12 years n=30	All n=59	2-5 years n=29	6-12 years n=30	All n=59	2-5 years n=29	6-12 years n=30
Mean	0.123	0.089	0.156	0.192	0.113	0.268	0.338	0.213	0.459
SD	0.272	0.218	0.317	0.291	0.165	0.362	0.429	0.293	0.504
Median	0	0	0	0.129	0	0.146	0.156	0	0.298
Range	0-1.13	0-0.78	0-1.13	0-1.53	0-0.51	0-1.53	0-1.70	0-1.00	0-1.70

* Includes all BEs between start of prophylactic treatment and last prophylactic treatment + 2 days or completion visit, whichever came first. BEs between start of treatment for surgery and re-start of prophylactic treatment after surgery were excluded. ** Number of BEs / (time in days between start of prophylactic treatment and last prophylactic treatment + 2 days or completion visit, whichever came first - days of surgery phases) x 30 days. BE = bleeding episode; PROPH = study population of patients receiving prophylaxis; SD = standard deviation.

6.2.3.13. Prophylactic treatment historical (pre-study) vs study

The study included a comparison between historical and on-treatment data (HJHS, dose, BEs). The results for the 53 patients out of the 59 patients in the PROPH population who received both pre-study (historical) and on-treatment (study) prophylactic FVIII treatment are summarised below in Table 29.

Table 29: GENA-03 - Comparison between historical (pre-study) and study (on-treatment) data for 53 patients in the PROPH population who received prophylactic treatment both pre-study and on-study.

Age	HJHS gait/total Historical	HJHS gait/total Study	Proph dose IU/kg/month Historical	Proph dose IU/kg/month Study	BEs/month Historical	BEs/month Historical
6.4 years	0.08/0.62	0.14/0.55	503.94	518.83	0.419	0.361

BE = bleeding episode; HJHS = haemophilia joint health score; IU = international units; Proph = dose administered for prophylaxis.

In the 53 patients (mean age 6.4 years) who received prophylactic treatment both pre-study and on-study the mean prophylactic doses of FVIII were similar (503.94 vs 518.83 IU/kg/month, respectively), but the monthly overall bleeding rate was approximately 15% lower at the end of the study (0.361 BEs/month) compared with the pre-study rate (0.419 BEs/month).

In the 53 patients treated prophylactically pre-study and on-study, the initial mean global gait score HJHS score was 0.08 at screening (historical) and increased to 0.14 at the end of the study. One patient who had an end-of-study gait score of 4 and a total score of 20 because he was bleeding in both ankles at the time of assessment skewed the end-of study results. This patient experienced a spontaneous bleed in his left ankle the day before the assessment and was actively bleeding in his right ankle on the day of his end-of-study HJHS assessment, which may account for the high HJHS. HJHS mean total scores for the 53 patients were similar at the screening and at end-of-study assessments (0.62 and 0.55, respectively).

In the total population with HJHS data (n=56), the mean±SD gait score was 0.1±0.32 at screening and 0.1±0.60 at final assessment, and the mean±SD total HJHS score was 0.8±2.03 at screening (range: 0, 11) and 0.6±2.78 (range: 0, 20) at final assessment. The majority of patients had HJHS scores of 0 at both screening and at final assessment (89.8% [53/56]).

6.2.3.14. Efficacy outcomes - treatment of breakthrough BEs

A total of 108 BEs (BLEED population) in 32 patients were treated with simoctocog alfa during the study (that is, between the start and end of prophylactic treatment plus 2 days, or study completion, whichever came first). Of the 108 BEs, 65 (60.2%) were traumatic, 36 (33.3%) were spontaneous and 7 (6.5%) were classified as “other”. Of the 108 BEs, 61 (56.5%) were minor, 46 (42.6%) were moderate to major and 1 (0.9%) was of unknown severity. There were no major to life-threatening bleeds. The frequency of treated BEs are summarised below in Table 30.

Table 30: GENA-03 - Frequency of treated BEs during the study; BLEED population, n=108 bleeds in 32 patients.

Frequency of BEs	N	%	Cumulative %
1	12	37.5	37.5
2	3	9.4	46.9
3	6	18.8	65.6
4	4	12.5	78.1
5	2	6.3	84.4
6	1	3.1	87.5
9	2	6.3	93.8
10	1	3.1	96.9
12	1	3.1	100

The most frequent sites of bleeding were the ankle (21 BEs) and the knee (15 BEs). Other affected sites were the elbow, leg, arm, oral cavity, nose and other sites (including the hip, finger, wrist, head, eye, chest, skin, iliac, shoulder, shin, hamstring, foot, toe, thumb, incised wound on a foot, lost tooth, tibia, buttock, jaw, site of uretero-cutaneostomy and a traumatic head bleed).

There were a total of 216 infusions administered to 32 patients with BEs. In the analysis summarised below in Table 31, when one infusion was given to treat several bleedings simultaneously the number of EDs and the number of dosages were counted only once.

Table 31: GENA-03 - EDs and simoctocog alfa (Human-cl rhFVIII) infusions for treatment of BEs; BLEED population, 108* BES (216 infusions) in 32 patients.

Parameter	Mean	SD	Median	Range
Number of EDs (for BEs)	1.9	1.85	1	1–10
Dose of *Human-cl rhFVIII* per BE, IU	2528	3716.2	1612.5	500–33,000
Dose of *Human-cl rhFVIII* per BE, IU/kg	95.9	169.3	43.9	25–1521
Number of infusions per BE	2.1	2.95	1	1–22
Dose of *Human-cl rhFVIII* per infusion, IU	1189	450.1	1000	500–3000
Dose of *Human-cl rhFVIII* per infusion, IU/kg	45.1	12.61	40.0	25–88

* Several simultaneous BEs are counted only once in this analysis, because the infusions for these BEs were given to treat several bleedings simultaneously. Thus, the number of EDs and the number of dosages are counted only once; thus number of infusions for this analysis was 216. BE = bleeding episode; BLEED = study population of BEs treated with simoctocog alfa; ED = exposure day; IU = international units; SD = standard deviation.

During the study, 68.6% of BEs were treated with one infusion and 81.3% of BEs with 1 or 2 infusions. Six (5.9%) BEs required 3 infusions, 4 (3.9%) BEs required 4 infusions, 2 BEs each (2.0% each) required 5, 6 and 8 infusions and 1 BE each (1.0% each) required 12, 15 and 22 infusions

The efficacy of on-demand treatment for BEs (breakthrough) occurring while on prophylactic treatment with simoctocog alfa in the BLEED population is summarised below in Table 32. Efficacy assessments were available for all 108 BEs treated with simoctocog alfa, 61 of which

were minor, 46 were moderate to major, and 1 unknown severity. On-demand treatment efficacy of simoctocog alfa in the two age subgroups (2–5 and 6–12 years) was comparable with the efficacy in the total population (2-12 years). On-demand treatment efficacy of simoctocog alfa in the BLEED-PP population was comparable to that in the BLEED population.

Table 32: GENA-03 - Efficacy assessment for treatment of BEs according to severity; BLEED population, 108 BEs in 32 patients.

Age	n	Bleed severity	Excellent n (%)	Good n (%)	Moderate n (%)	None n (%)
All: 2-12 years	108	Any BE	77 (71.3(	12 (11.1)	17 (15.7)	2 (1.9)
	61	Minor BE	53 (86.9)	7 (11.5)	1 (1.6)	0
	46	Moderate-Major BE	23 (50.0)	5 (10.9)	16 (34.8)	2 (4.3)
Age: 2-5 years	33	Any BE	21 (63.6)	6 (18.2)	6 (18.2)	0
	20	Minor BE	15 (75.0)	5 (25.0)	0	0
	13	Moderate-Major BE	6 (46.2)	1 (7.7)	6 (46.2)	0
Age: 6-12 years *	75	Any BE	56 (74.7)	6 (8.0)	11 (14.7)	2 (2.7)
	41	Minor BE	38 (92.7)	2 (4.9)	1 (2.4)	0
	33	Moderate-Major BE	17 (51.5)	4 (12.1)	10 (30.3)	2 (6.1)

* The severity of 1 BE ([information redacted], 6–12 years subgroup) was classed as unknown and had an efficacy rating of excellent. BE = bleeding episode; BLEED = study population of BEs treated with simoctocog alfa; n = number analysed.

The IDMC adjudicated on all personal efficacy assessments for the treatment of BEs, primarily considering the number of infusions administered for each BE. In 3 cases the IDMC efficacy assessment differed from the personal efficacy assessment. In 1 case in which the personal assessment was rated “good”, efficacy was judged “moderate” by the IDMC; in 1 case in which the personal assessment had been “excellent”, efficacy was rated “good” by the IDMC; and in 1 case in which the personal assessment was rated “moderate”, efficacy was judged “none” by the IDMC (during the final IDMC meeting for this study after database lock).

6.2.3.15. Surgery

Six patients (including 1 with VWD) underwent 6 planned major surgical procedures and received prophylactic simoctocog alfa (see Table 33, below).

Table 33: GENA-03 - Surgical procedures; SURG population, 6 surgeries in 6 patients.

Description of surgery	Infusions (N)	EDs (N)	Total dose IU/kg	Overall efficacy rating
Port catheter implantation	20	7	593.22	Excellent
Circumcision	5	3	183.33	Excellent
Port catheter replacement	3	2	150.00	Excellent
Port catheter implantation	5	4	233.33	Excellent
Port catheter implantation	4	3	170.00	Excellent
Port catheter implantation	4	2	160.00	Not assessed*

* This patient was later diagnosed with von Willebrand disease and withdrawn from the study. ED = exposure day; IU = international units; SURG = study population of surgeries treated with simoctocog alfa.

EDs and dosages administered for all 6 patients in the SURG population (including the patient with VWD) are summarised below in Table 34. Excluding the patient with VWD [information redacted], individual doses for the 5 surgeries ranged from 28.25 IU/kg to 56.50 IU/kg. All 5 patients received a 50 IU/kg loading dose before surgery, except patient [information redacted] who received 56.50 IU/kg. No maintenance doses during surgery were required for any patient. The number of infusions ranged from 3 to 5 and the number of EDs ranged from 2 to 4, with the exception of one patient [information redacted] who underwent a port catheter implantation and received 20 infusions during 7 EDs. There was no special explanation given by the investigator for the high number of infusions in this patient, except that according to her experience it is possible for this kind of procedure. No BEs were documented for this patient during this time period, and it was stated that the procedure went well without any complication. Blood loss during all these surgeries was minimal (2–10 mL), with the highest amount of 10 mL each for a port catheter implantation [information redacted] and a circumcision [information redacted]. One port catheter implantation surgery [information redacted] had higher than average expected blood loss, however, the actual blood loss was very low (4 mL) and not higher than the maximum expected blood loss (5 mL). Efficacy was rated as excellent by both the surgeon and the haematologist for all 5 surgeries. One patient [information redacted] was treated with tranexamic acid during the hospitalisation after surgery. The mean duration of the surgical procedures was 33.3±6.06 minutes, ranging from 30 to 45 minutes. The mean expected duration was 40 minutes for all surgical procedures.

Table 34: GENA-03 - EDs and dosages administered for surgeries; SURG population, 6 surgeries in 6 patients.

ED = exposure day; IU = international units; SD = standard deviation; SURG = study population of surgeries treated with simoctocog alfa (Human-cl rhFVIII).

6.2.3.16. Concomitant treatments after the start of prophylactic treatment

Forty (40) patients received at least one concomitant medication after the start of prophylactic treatment. The most frequently used medication classes (except for surgery) were anti-haemorrhagics in 33 patients, antibacterials in 16 patients and analgesics in 12 patients One analgesic (paracetamol) was used during 1 of 6 surgeries. No patients received blood transfusions or blood cell concentrates during the study.

Thirty-three (33) patients received anti-haemorrhagic treatment, including pdFVIII and rFVIII concentrates, tranexamic acid and von Willebrand factor. The 33 patients include the 24 patients who had received their previous FVIII concentrate as part of PK analysis (PK Cycle 1). Thirteen (13) patients received anti-haemorrhagics other than simoctocog alfa for reasons other than PK analysis. Eight (8) patients received other FVIII concentrates as part of their previous prophylaxis after being enrolled into the study, but before their prophylactic regimen with simoctocog alfa had begun. Three (3) patients who received other FVIII concentrates after the start of prophylaxis are described in the paragraphs below.

One patient received 12 infusions of simoctocog alfa over 10 days for a moderate to major bleed in his right ankle. The next day he started receiving a pdFVIII and was excluded from the study due to treatment failure. Efficacy of simoctocog alfa treatment for this BE was rated as none,

One patient received 500 IU of a pdFVIII/vWF twice for a moderate to major bleed that was related to his surgery (port catheter implantation). Prior surgery, he received 4 infusions over 2 EDs of simoctocog alfa and the efficacy of these was judged as none. This patient was later withdrawn from the study because he was diagnosed with VWD.

One patient received one infusion of 1000 IU of a pdFVIII for a minor traumatic bleed in his left elbow because he did not have any simoctocog alfa when the bleeding started. Over the subsequent 8 days he was treated with simoctocog alfa and treatment for this BE with simoctocog alfa was rated as good.

6.3. Studies providing supportive efficacy data

6.3.1. GENA-09 - adult patients aged 18 to 62 years

6.3.1.1. Overview of the study

GENA-09 was designed as a prospective, open-label, single-country (Russia), single-centre, Phase II study in PTPs with severe haemophilia A (FVIII:C ≤ 1%). It included a randomised cross-over PK part (Part I) and an uncontrolled efficacy part (Part II). The results for the PK part of the study have been reviewed in the *Pharmacokinetics* section of this CER. The study was undertaken between 16 March 2009 and 26 May 2010, and the CSR (final analysis) was dated 14 December 2010. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and ICH-GCP (Note for Guidance CPMP/ICH/135/95). The study was sponsored by Octapharma, Switzerland.

The primary objective of this study was to determine the PK profile of simoctocog alfa and to compare it with the PK profile of a full-length rFVIII. The secondary objectives were to calculate the incremental recovery of FVIII:C for simoctocog alfa, to investigate the immunogenicity of simoctocog alfa, and to assess the clinical efficacy and safety of simoctocog alfa during prophylactic treatment, breakthrough BEs, and in surgical prophylaxis.

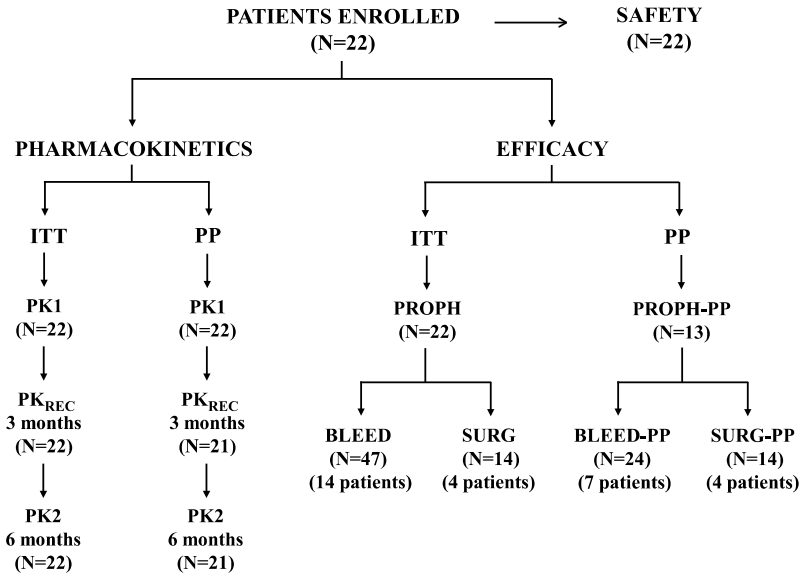
The efficacy endpoints in the study were identical to those in GENA-01, GENA-08, and GENA-3. The statistical analysis of the primary, secondary and safety endpoints was exploratory. No confirmatory hypothesis testing was planned. No formal sample size calculation was undertaken. The planned sample of 22 patients was chosen to satisfy applicable CHMP and FDA recommendations.

The study included adult male patients with severe haemophilia A (FVIII:C ≤ 1%) aged ≥ 18 to ≤ 65 years with a body weight of 45 to 110 kg. Overall, the inclusion and exclusion criteria were consistent with GENA-01 and GENA-08. Patients who completed Part 1 (cross-over PK) of the study were then eligible to enter Part 2 (efficacy and safety) of the study for a period of 6 months and for at least 50 EDs with simoctocog alfa for prophylaxis (PROPH population). The efficacy of simoctocog alfa for the treatment of breakthrough BEs (BLEED population) and for surgical prophylaxis (SURG population) was also assessed in Part 2 of the study.

Patients treated prophylactically with simoctocog alfa received 30 + 5 FVIII IU/kg every other day until 6 months and ≥ 50 EDs were reached. Two dose escalations (each + 5 IU/kg) were allowed in case of inadequate response defined as ≥ 2 spontaneous BEs during one month. The required dosage was determined by the same formula as used in GENA-01. Patients were supplied with a sufficient amount of simoctocog alfa for home treatment. The required target peak FVIII levels for treatment of breakthrough BEs were the same as for GENA-01. Minor haemorrhage was treated with 10-20 IU FVIII/kg every 12-24 hours until BE resolution. Moderate to major haemorrhage was treated with 15-30 IU FVIII/kg repeated every 12-24 hours until BE resolution. Major to life threatening haemorrhage was treated with an initial dose of 40-50 IU FVIII/kg with repeat doses of 20-25 IU FVIII/kg every 8-12 hours until BE resolution. The dosage regimens of simoctocog alfa for surgical prophylaxis were identical to those for GENA-01.

The patient disposition of the 22 enrolled patient is summarised below in Figure 8. Protocol deviations were recorded for 21 of the 22 patients (95.5%) in the PK-PP and SAFETY populations. Major protocol deviations were recorded in 9 of the 22 patients (40.9%). All major protocol deviations were due to a time interval ≥ 5 days between 2 doses after the start of prophylactic treatment with simoctocog alfa, which occurred twice in 7 patients and once in 2 patients and did not impact on the aims or outcomes of the study. Minor protocol deviations were recorded for 20 of the 22 patients (90.9%) patients.

Figure 8: GENA-09 - Patient disposition.



The baseline demographic characteristics of the 22 enrolled patients are summarised below in Table 35.

Table 35: GENA-09 - Baseline demographic and clinical characteristics

Parameter	Mean	SD	Median	Range
Age at first treatment (years)*	24.5	9.77	21.0	18–62
Height (cm)	177.5	6.58	178.0	166–191
Weight (kg)	69.0	13.82	65.0	50–105
Time since diagnosis (years)	22.93	10.032	19.80	11–61
FVIII:C (IU/mL) (CHR)	0.013	0.0138	0.014	0–0.05
FVIII:C (IU/mL) (OS)	0.010	0.0202	0	0–0.06
HJHS (Gait)	2.5	1.01	3.0	0–4
HJHS (Total)	45.3	20.42	45.0	17–82

*With Simoctocog alfa. CHR = Chromogenic, FVIII:C = FVIII coagulant activity, HJHS = Haemophilia Joint Health Score, OS = One-stage.

Comment: The mean±SD age of patients in this study was 24.5±9.77 years and the range was 18 to 62 years. The mean HJHS gait score was high (2.5) with expected ranges from 0 (best) to 4 (worst), as was the HJHS total score (45.3) with expected ranges of from 0 (best) to 148 (worst). The HJHS scores suggest that the patients in this study had severe joint disease. The sponsor states that it is noteworthy that GENA-09 is the first clinical study to systematically evaluate the efficacy of FVIII prophylaxis in such a severe adult patient population who had been inadequately treated since childhood.

6.3.1.2. Results - routine prophylaxis

A total of 22 patients received prophylactic treatment with simoctocog alfa. The number of EDs and dosage of simoctocog alfa administered as prophylaxis in the PROPH population are shown below in Table 36.

Table 36: GENA-09 - EDs and dosage in patients receiving prophylaxis with simoctocog alfa; PROPH population, n=22.

Parameter	Mean	SD	Median	Range
Number of EDs	90	9.06	89.5	75–123
Number of dosages administered per ED	1.0	0	1.0	1–1
Duration of prophylactic treatment, months	6.3	0.4	6.1	6.0–7.7
Average amount of Human-cl rhFVIII, per month, IU/month	32,419	7,309	30,498	22,097–47,085
Average amount of Human-cl rhFVIII per injection, IU	2,272	531	2,030	1,500–3,500
Average amount of Human-cl rhFVIII per injection, IU/kg	32.8	2.3	33.2	27.7–36.6

A total of 48 BEs occurred between the first prophylactic treatment and final assessment (47 requiring treatment with simoctocog alfa and 1 not requiring treatment). Of the 22 patients who received prophylactic treatment, 14 (63.6%) experienced at least one BE and 8 (36.4%) experienced no BEs. Of the 14 patients experiencing a BE, 5 patients experienced 1 BE, 3 patients experienced 2 BEs, 2 patients experienced 7 BEs, and 1 patient each experienced 3, 4, 5, and 11 BEs.

In the 22 patients treated with prophylactic simoctocog alfa, the mean±SD number of BEs

during treatment was 2.2±2.9 (95% CI: 0.9, 3.5) with a range of 0 to 11, and the mean±SD monthly rate of BEs was 0.345±0.472 (range: 0, 1.76). The overall efficacy ratings of prophylactic treatment with simoctocog alfa were: excellent in 81.8% (18/22) of patients (that is, BEs/month < 0.75); good in 4.5% (1/22) of patients (that is, BEs/month > 0.75 - 1); moderate in 9.1% (2/22) of patients (that is, > 1 - 1.5 BEs/month); and poor in 4.5% (1/22) of patients (that is, > 1.5 BEs/month). For spontaneous bleeds, efficacy of simoctocog alfa prophylaxis was excellent in 18 (81.8%) patients, good in 2 patients (9.1%), and moderate in 2 (9.1%) patients with no patients having poor efficacy.

The mean±SD monthly rate of spontaneous and traumatic BEs in the 22 patients receiving simoctocog alfa prophylaxis was 0.244±0.414 (range: 0, 1.44) and 0.093±0.1366 (range: 0, 0.48). Prophylaxis efficacy for traumatic BEs was excellent in 100% (22/22) of patients. Prophylaxis efficacy for spontaneous BEs was excellent in 81.8% (18/22) of patients, good in 9.1% (2/22) of patients and moderate in 9.1% (2/22) of patients.

The historical (pre-study) mean monthly rate of BEs was high, as expected in this inadequately pretreated population, but was reduced at the end of the study in all 22 patients (1.916 BEs/month [pre-study] vs 0.345 BEs/month [during the study]). In 15 patients who had received prior FVIII prophylaxis the rate of BEs fell by approximately 71% from a mean of 1.152 per month prior to study to a mean of 0.337 per month during prophylaxis with simoctocog alfa. However, the sponsor states that it is likely that historical BE rates are underestimated as a value of zero was assumed for 7 patients for whom historical data were not available. The mean dose of FVIII increased by approximately 61% during the prophylaxis period with simoctocog alfa (468 IU/kg/month) compared with pre-study FVIII doses (290 IU/kg/month). In 7 patients treated on-demand for BEs prior to the study (6 patients treated with FVIII and 1 patient treated with cryoprecipitate), the average monthly BE rate was reduced from 3.55 BEs/month pre-study to 0.36 BEs/during the study.

6.3.1.3. Results - treatment of break-through BEs

A total of 47 breakthrough BEs (BLEED population) were treated with simoctocog alfa in 14 patients receiving prophylaxis with simoctocog alfa. Eight (8) patients had no bleeds, 5 patients had 1 BE, 3 patients had 2 BEs, 1 patient had 3 BEs, 1 patient had 4 BEs, 1 patient had 5 BEs, 1 patient had 6 BEs, 1 patient had 7 BEs, and 1 patient had 11 BEs. Of the 47 BEs, 33 (70.2%) were spontaneous, 13 (27.7%) were traumatic, and 1 (2.1%) was categorised as "other" (associated with physical activity). For all sites, the severity of the BE was minor in 36.2% (17/47) of cases and moderate to major in 63.8% (30/47) of cases, and there were no major or life threatening BEs.

The mean±SD number of EDs for bleedings was 1.9±1.22 and the median was 1.0 (range: 1, 6). The mean±SD number of infusions was 2±1.7 and the median was 1.5 (range: 1, 6). The mean±SD dose of simoctocog alfa per infusion was 32.6±5.9 IU/kg and the median dose was 32.8 (range: 8, 50) IU/kg. The mean±SD dose/ED for the 17 minor BEs was 32.7 IU/kg, and the mean±SD dose/ED for the 30 moderate to major BEs was 32.9 IU/kg.

Overall, 29 (61.7%) BEs were treated with excellent or good efficacy (29.8% [14/47] and 31.9% [15/47], respectively), while efficacy was rated as moderate in the remaining cases (38.3% [18/47]). For treated minor BEs (n=17), efficacy was reported as excellent or good for 16 (94.1%) BEs (58.8% [10/17] and 35.2% [6/17], respectively), while efficacy was rated as moderate for the remaining case (5.9% [1/17]). For treated major BEs (n=30), efficacy was rated as excellent or good for 11 (43.3%) BEs (13.3% [4/30] and 30.0% [9/30], respectively), while efficacy was rated as moderate in the 17 remaining cases (56.7% [17/30]). No treated BEs were rated as having no efficacy.

6.3.1.4. Results - surgery

Four (4) patients underwent a total of 14 minor surgical procedures (11 planned, 3 emergency). The mean duration (range) of the surgical procedures was 9.5 (5, 15) minutes and similar to the

expected duration of 10 minutes. Concomitant hyaluronate was used during 4 surgical procedures, hydrocortisone in 7 procedures, and triamcinolone in 1 procedure.

In 13 of the 14 surgical procedures, a single dose of simoctocog alfa was administered prior to surgery, while 2 doses were administered to one patient who received a second infusion after the end of surgery (2000 IU, 28.57 IU/kg). No maintenance doses were administered. The mean loading dose was 2,535.7 IU (range: 2000, 3000) corresponding to 35.26 IU/kg (range: 28.2, 50.0).

The 14 surgical procedures in the 4 patients were: 1 patient - three procedures (all "punctures" of the left knee) with 1 infusion for 2 procedures and 2 infusions for 1 procedure, the infusions ranged from 28.17 to 35.71 IU/kg; 1 patient - 9 procedures (5 "punctures" of the right knee, 4 "punctures" of the left ankle) with each procedure requiring 1 infusion (33.33 IU/kg); 1 patient - 1 procedure ("puncture" of the left ankle) requiring 1 infusion (34.88 IU/kg); and 1 patient - 2 procedures (both tooth extraction) each requiring 1 infusion (50.00 IU/kg). The efficacy rating for simoctocog alfa was excellent for all 14 minor surgical procedures, as rated by both the surgeon and the haematologist.

6.3.2. GENA-04 (extension study to GENA-09) - adults aged 18 to 62 years.

6.3.2.1. Overview of the study

GENA-04 was designed as a prospective, single-centre, uncontrolled, open-label, Phase IIIb safety and tolerability extension study for patients who had successfully completed GENA-09. The study was initiated on 21 November 2009 and terminated on 28 July 2011, and the CSR was dated 22 March 2012. The study was originally planned to continue until simoctocog alfa was registered and launched in Russia. However, due to substantial changes in data requirements introduced by the Russian regulatory authorities, the study centre was instructed in early 2011 to continue the study only until their supplies of simoctocog alfa were used up. The study was terminated on 28 July 2011 after a mean of 226 exposure days (EDs) per patient. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and ICH-GCP (Note for Guidance CPMP/ICH/135/95), and national regulatory requirements. The study was sponsored by Octapharma, Switzerland.

The primary objectives of the study were to investigate the long-term immunogenic potential and the long-term tolerability of simoctocog alfa. The secondary objectives of the study were: to determine the long-term efficacy of simoctocog alfa during prophylactic treatment, for treatment of BEs and for surgical prophylaxis in PTPs with severe haemophilia A, and to calculate the long-term incremental recovery of FVIII:C for simoctocog alfa.

The efficacy endpoints of the study were the same as those for GENA-09. The statistical analysis of all endpoints was exploratory. No confirmatory hypothesis testing was planned. No formal sample size calculation was undertaken.

Eighteen (18) patients who had already completed GENA-09 were included in this extension study. Simoctocog alfa was administered to all patients prophylactically, for treatment of BEs or for surgical procedures. Patients being treated prophylactically received 30 + X IU FVIII/kg BW every other day until study completion. As only entire vials were infused, patients may have received slightly more than 30 IU/kg; 'X' represents this difference. Two dose escalations of + 5 IU/kg BW each were allowed in case of an inadequate response defined as >2 spontaneous BEs during one month.

The treatment of breakthrough BEs in GENA-04 differed from those in GENA-09 due to a protocol amendment. After review of all data from the interim analysis performed for the initial GENA-09 study, the IDMC recommended adapting the dose recommendations given in the original protocol for the treatment of BEs. Minor breakthrough BEs were treated with 20-30 IU FVIII/kg BW (rather than 10-20 IU FVIII/kg BW in GENA-09) repeated every 12-24 hours. Moderate to major breakthrough BEs were treated with 30-40 IU FVIII/kg BW (rather than 15-

30 IU FVIII/kg BW in GENA-09) repeated every 12-24 hours. Major to life-threatening breakthrough BEs were treated with an initial dose of 50-60 IU FVIII/kg BW (rather than 40-50 IU FVIII/kg BW in GENA-09) with repeat doses of 20-25 IU FVIII/kg BW (same dose as GENA-09) every 8-12 hours. The doses used for prophylactic and surgical procedures were identical to those used in GENA-09.

The efficacy population included 18 enrolled patients, all of whom were included in the ITT population. All 18 patients in the ITT population were included in the simoctocog alfa prophylactic population (PROPH) and 9 patients in this population experienced 37 breakthrough BEs and were included in the BLEED population. Of the 9 patients in the BLEED population (37 BEs), 8 patients experienced 36 spontaneous BEs and 1 patient experienced 1 traumatic BE. The PP efficacy population included 16 patients in the PROPH-PP population and 9 patient in the BLEED-PP population (identical to the BLEED population). The surgical population (SURG) included 3 patients who had undergone 7 surgical procedures. The SAFETY population included 18 patients and was identical to the ITT population.

Major protocol deviations were reported in 2 patients in the ITT/Safety population and these 2 patients were excluded from the PP population (1 withdrew consent; 1 had > 1 treatment (gap defined as ≥ 5 days without treatment) per year. Seven (7) patients had minor protocol deviations and all of these patients were included in the PP population.

The mean±SD age of the patients was 25.8±10.6 years with a median of 22.5 years (range: 18, 62), and the mean±SD weight was 73.0±14.4 kg with a median of 72.5 kg (range: 55, 110).

6.3.2.2. Results - prophylaxis

All 18 enrolled patients treated with prophylactic simoctocog alfa were included in the efficacy analysis. The mean±SD number of prophylactic exposure days (and the total number of infusions) was 219±63 (range: 14, 283). The mean±SD dose of simoctocog alfa per infusion was 34.6±3.9 IU/kg (range: 31.1, 45.3), and the mean±SD amounts administered per month of the study was 497±66 IU/kg (range: 396, 664) and per year of the study was 6,049±808 IU/kg (range: 4825, 8088).

Of the 18 patients treated with prophylactic simoctocog alfa, 9 patients experienced a total of 37 BEs (36 spontaneous BEs in 8 patients; 1 traumatic BE in 1 patient). Ten (10) patients did not experience any spontaneous BEs, 3 patients experienced 1 spontaneous BE, 2 patients experienced 5 spontaneous BEs, and 1 patient each experienced 3, 4, and 16 BEs. The mean±SD number of spontaneous breakthrough BEs per month in the 18 patients treated with prophylactic simoctocog alfa was 0.11±0.21 (range: 0, 0.86). The efficacy of prophylactic treatment with simoctocog alfa was rated as excellent (< 0.75 BEs/month) in 17 (94%) patients and good (0.75-1 BEs/month) in 1 (6%) patient.

The majority of the 37 BEs occurred in the knees (22 BEs, including one due to trauma). Bleeding was also noted in the elbows (6), ankles (4), arm (1), oral cavity (1) and other sites (including 2 episodes of haematuria and 1 back muscle bleed). Of the 37 BEs, 20 (54%) were considered minor and 17 (46%) were considered moderate to major. Of the 22 BEs occurring in the knee, 15 were minor and 7 were moderate to major. Overall, the mean±SD duration of the BEs (n=37) was 1.34±1.89 days with a median of 1.89 days (range: 0.03, 8.74).

Of the 13 patients (mean age 22.6 years) who had received pre-study (historical) prophylactic FVIII treatment and prophylactic treatment with simoctocog alfa during the study, the mean number of BEs/month decreased approximately 87% from 1.108 (pre-study GENA-09) to 0.143 (during GENA-04), and the mean FVIII dose per month increased approximately 64% from 307.5 to 503.9 IU/kg. In these 13 patients, the mean HJHS (gait/total) scores improved from 2.5/43.2 (pre-study GENA-09) to 1.9/33.8 (end of study GENA-04).

Of the total number of 18 patients (mean age 25.8 years) treated with prophylactic simoctocog alfa during GENA-04 (13 who had received prophylactic FVIII and 5 who had been treated on

demand prior to GENA-09), the mean number of BEs/month decreased by approximately 94% from 1.820 (pre-study GENA-09) to 0.118 (during GENA-04), and the mean FVIII dose per month increased approximately 61% from 222.1 to 496.8 IU/kg. In these 18 patients, the mean HJHS (gait/total) scores improved from 2.6/46.5 (pre-study GENA-09) to 1.9/36.9 (end of study GENA-04).

6.3.2.3. Results - treatment of bleeding episodes

During the study period, 9 (50%) patients experienced 37 breakthrough BEs treated with simoctocog alfa, and a total of 75 infusions were administered over 66 EDs for the treatment of these BEs. The mean±SD number of exposure days for BEs was 7.33±6.75 with a median of 5 days (range: 1, 8), and the mean±SD number of infusions for treatment of BEs was 8.33±8.51 with a median of 5 infusions (range: 1, 24). The mean±SD number of infusions needed to stop a BE was 2.03±2.33 with a median of 1 infusion (range: 1, 12). The mean±SD dose per infusion was 34.63±5.44 IU/kg with a median dose of 35.71 IU/kg (range: 23.67, 43.73).

The majority of BEs were treated for 1 or 2 days (31/37, 84%), while 2 BEs each required 3 and 6 days of treatment and 1 BE each required 4 and 7 days. The mean duration of treatment was 1.78 days and, on average, moderate to major bleeding required longer treatment than minor bleeding (2.65 days vs 1.05 days, respectively). The mean number of infusions needed to stop the bleeding was approximately 2 (range: 1, 12). The highest number of infusions (12) was administered for the treatment of haematuria in 1 patient.

Overall, the efficacy of simoctocog alfa for the treatment of BEs was rated as excellent for 37.8% (14/37) of BEs, good for 45.9% (17/37) of BEs, moderate for 8.1% (3/37) of BEs, and none for 8.1% (3/37) of BEs. The efficacy of treatment for minor BEs was rated as excellent or good for all 20 BEs (14 [70%] excellent; 6 [30%] good). The efficacy of treatment for the 17 moderate to major BEs was rated as excellent for none, good for 11 (64.7%), moderate for 3 (17.6%) and none for 3 (17.6%). The 3 moderate to major bleeds for which treatment efficacy was rated as none occurred in 2 patients (haematuria in 1, and a knee and ankle bleed in 1 patient). The patient with haematuria experienced 2 additional BEs before and after the haematuria, which were both treated with moderate efficacy. The patient with the joint bleeds subsequently experienced 2 further BEs for which efficacy ratings were good.

6.3.2.4. Efficacy - surgery

Three (3) patients underwent a total of 7 surgical procedures, all of which were planned. Of the 7 surgical procedures, 3 (42.9%) were major (1x total THR and 1x revision THR in 1 patient; 1x TKR in 1 patient), and 4 (57.1%) were minor (3x "punctures" left knee in 1 patient). The mean duration of the surgical procedures was 1.2 hours (range: 0.25, 3.22), and was similar to the expected duration of 1.51 hours. All minor surgical procedures required only 1 infusion on 1 exposure day, while the 3 major surgeries required, on average, approximately 30 infusions (range: 23, 35) over 17 EDs (range: 15, 20). Major surgeries required higher doses of simoctocog alfa per exposure day than minor surgeries (73.38 vs 41.07 IU/kg, respectively).

All patients received a loading dose of simoctocog alfa, and the mean±SD loading dose was 47.0±7.9 IU/kg (range: 35.7, 55.6). The patient undergoing TKR required an additional infusion of 55.6 IU/kg during surgery, which was administered 2.5 hours after the start of the procedure. During the post-surgical period the mean dose of simoctocog alfa was 40.14 IU/kg. Major surgical procedures required higher doses of simoctocog alfa per ED than minor surgical procedures (73.4 vs 41.1 IU/kg, respectively).

Blood loss was not observed during any of the minor surgical procedures. Actual blood loss for the major procedures was lower than the expected blood loss (1,033 vs 1,250 mL, respectively). All 3 major surgeries required the transfusion of FFP or erythrocyte concentrate.

Intra-operative efficacy for all 7 surgical procedures was rated as excellent by the surgeon. The overall efficacy was rated as for excellent for the 4 minor surgical procedures and as good for the 3 of the major surgical procedures by the surgeon and haematologist.

6.4. Analysis performed across trials

There were no meta-analyses or pooling of data across studies.

6.5. Evaluator's conclusions on clinical efficacy

The submitted data are considered to have satisfactorily established the efficacy of simoctocog alfa for routine prophylaxis against BEs, treatment of breakthrough BEs while on prophylaxis and surgical prophylaxis in previously treated children aged 2 to 12 years and adults with severe haemophilia A. The submission provided efficacy data from 135 patients treated with simoctocog alfa, including 76 patients aged > 12 years and 59 patients aged 2 to 12 years.

The submission included five completed clinical studies with efficacy data (GENA-01, GENA-08, GENA-03, GENA-09 and GENA-04). Of these five studies, three, multinational (predominantly Western countries), multicentre studies were nominated by the sponsor as providing primary efficacy data (GENA-01, GENA-08, GENA-03), and the single centre Russian study GENA-09 and its extension GENA-04 were nominated as providing supportive efficacy data. Therefore, for efficacy and safety GENA-01, GENA-08, and GENA-03 can be considered to be pivotal studies and GENA-09 and GENA-04 can be considered to be supportive studies.

The five clinical studies were conducted in accordance with the recommendations of the latest EMA *Guideline on the Clinical Investigation of Recombinant and Human Plasma-Derived Factor VIII Products (EMEA/CHMP/BPWP/ 144533/2009).* Overall, this guideline is more stringent than the previous EMA *Note for Guidance on the Clinical Investigation of Recombinant Factor VIII and IX products (CPMP/BPWG/1561/99)*. All studies enrolled patients who had been previously treated with FVIII products (defined as having ≥ 150 EDs in patients at least 12 years of age, and ≥ 50 EDs in patients less than 12 years of age). In addition, the study duration per patient was the same in all studies (that is, at least 6 months and at least 50 EDs).

GENA-08, GENA-03, GENA-09 and GENA-04 investigated the efficacy of simoctocog alfa for routine prophylaxis, the treatment of breakthrough bleeding occurring during prophylaxis and for surgical prophylaxis. GENA-01 investigated the efficacy of simoctocog alfa for the on-demand treatment of BEs and for surgical prophylaxis, but not for routine prophylaxis. In GENA-01, GENA-08, GENA-09, and GENA-04, all patients had at least 150 previous EDs, and paediatric patients in GENA-03 had at least 50 EDs. GENA-04, the long-term extension study, was terminated after a mean of 226 EDs of routine prophylaxis. The relevant TGA adopted EMA guideline recommends that for FVIII products at least 50 PTPs aged > 12 years should be followed for at least 50 EDs or 6 months whichever is sooner, and that at least 20 children under the age of 6 years (irrespective of previous treatment) should be studied. However, the adopted TGA guideline specifies that the mandatory study in children may be submitted after marketing authorization is granted. Overall, patient numbers and exposure to simoctocog alfa are greater than required by the relevant TGA adopted guideline.

The inclusion and exclusion criteria were similar for all five clinical studies. All patients were males with severe haemophilia A (FVIII:C <1%). The inclusion criteria stipulated that all patients were required to be immuno-competent (CD4+ lymphocytes >200/µL), and negative for HIV or if positive have a viral load of less than 200 particles/µL or less than 400,000 copies/mL. Therefore, patients could be HIV positive provided that they met the inclusion criteria relating to immuno-competence and viral load/viral particles. The studies excluded patients with coagulation disorders other than haemophilia A, patients with present or past FVIII inhibitory activity over 0.6 BU, patients with severe liver or kidney disease and patients

receiving immuno-modulating drugs. Overall, the inclusion and exclusion criteria are considered to be satisfactory and representative of Australian patients likely to be offered treatment with simoctocog alfa.

GENA-01 planned to recruit patients of at least 12 years of age, but only 2 of the 22 enrolled patients were actually under 18 years of age. GENA-08 also planned to include adolescents over 12 years of age, but none of the 32 enrolled patients were younger than 18 years of age. In GENA-09, all 22 enrolled patients were at least 18 years of age and 18 of these patients subsequently enrolled in GENA-04 (extension study to GENA-09). In GENA-03, all 59 enrolled patients were aged between 2 and 12 years (29 aged from 2-6 years; 30 aged from 6-12 years). Overall, the studies included 2 adolescent patients aged older than 12 years and younger than 18 years. No patients under the age of 2 years or older than 75 years of age were included in the studies. The key baseline characteristics of the study populations in the five submitted studies are summarised below in Table 37.

Table 37: Key baseline characteristics expressed as mean (range) unless otherwise stated for patients in the 5 submitted clinical studies.

Parameter	GENA-01 (n=22)	GENA-08 (n=32)	GENA-03 (n=59)	GENA-09 (n=22)	GENA-04 (n=18) *
Age [years]	39.6 (12–65)	37.3 (18–75)	6.1 (2–12)	24.5 (18–62)	25.83 (18–62)
Height [cm]	174 (154-188)	178 (158-192)	123 (82-173)	178 (166-191)	N/A
Weight [kg]	73 (46-105)	83 (47-127)	27 (8-73)	69 (50-105)	73 (55-110)
Race [% White]	81.8%	90.6%	100%	100%	100%
HJHS (gait)	1.6 (0-4)	1.6 (0-4)	0.1 (0-2)	2.5 (0-4)	2.6 (0-4)
HJHS (total)	38.4 (0-84)	34.6 (0-117)	0.8 (0-11)	45.3 (17-82)	46.5 (17-82)
FH of HA (%)	63.6%	56.3%	40.7%	54.5%	Not Applicable
FVIII inhibitors**	0%	0%	0%	0%	Not Applicable

* All 18 patients in GENA-04 participated in GENA-09. ** FVIII inhibitors (< 0.6 BUs). FH of Haem A = Family history of haemophilia A.

6.5.1. Prophylaxis

The efficacy of routine prophylaxis with simoctocog alfa was assessed in two of the three pivotal studies (GENA-08 and GENA-03) and in the two supportive studies (GENA-09 and GENA-04). A total of 113 patients received prophylactic treatment with simoctocog alfa every other day, while in GENA-03 prophylaxis could also be administered to paediatric patients 3 times per week. The majority of the 113 patients were from two of the three pivotal studies GENA-08 and GENA-03 (80.5% [n=91]) with the remainder coming from the two supportive studies GENA-09 and GENA-04 (19.5% [n=22]). Prophylactic treatment across the two pivotal studies with data is summarised below in Table 38.

Table 38: Summary of prophylactic treatment.

	GENA-08 (n=32)	GENA-03 (n=59)	GENA-09 (n=22)	GENA-04 (n=18) *
Administered Dose	30-40 IU/kg ever other day	30-40 IU/kg every other day or 3x/wk	30 + 5 IU/kg every other day	30 + X IU/kg every other day
Mean Dose (range) IU/kg	32.8 (24.0, 39.3)	38.9 (26.0, 56.7)	32.8 (27.7, 36.6)	34.6 (31.1, 45.3)
Number of EDs (mean±SD)	85.1±15.4	89.8±22.33	90±9.1	219±6.3
Patients without BE, n (%)	16 (50.0%)	27 (45.8%)	8 (36.4%)	10 (55.6%)
Patients with ≥ 1 BE, n (%)	16 (50.0%)	32 (54.2%)	14 (63.6%)	8 (44.4%)
Spontaneous BEs/month	0.095 (range: 0, 0.71)	0.123 (range: 0, 1.13)	0.24 (range: 0, 1.44)	0.11 (range: 0.1, 0.86)
Traumatic BEs/Month	0.082 (range: 0, 0.68)	0.192 (range: 0, 1.53)	0.093 (range:0, 0.48)	Not Available **
All BEs/month	0.188 (range: 0, 1.21)	0.338 (range: 0, 1.70)	0.345 (range:0, 1.76)	Not Available **

Notes: * All patients in GENA-04 also participated in GENA-09. ** Only 1 traumatic BE occurred in this study. GENA-08, BEs were assessed between visit 1 and study completion visit. GENA-03 and GENA-09, BEs assessed between start and end of prophylactic treatment phase. GENA-04, spontaneous BES between the start and the end of the prophylactic treatment phase (only one traumatic BE occurred in this study).

The mean number of EDs ranged from approximately 85 to 90 across GENA-08, GENA-03, and GENA-09, while the mean number of EDs for GENA-04 was 219 (see Table 38 above). The percentage of patients experiencing BEs while on prophylaxis ranged from 44% to 64%, and was highest in GENA-09 followed by GENA-03. The sponsor comments that the relatively high number of BEs in GENA-09 might be attributed to pre-existing severe joint damage due to

inadequate previous treatment of the adult patients in this study, whereas in GENA-03 the relatively high number of BEs might be due to an increased risk of accidents or falls in the paediatric patients in this study. In addition, it is possible that the lower potency of vials used in GENA-09 may have contributed to higher BE rates. The sponsor's explanations for the findings in GENA-09 and GENA-03 are not unreasonable. Of note, the BE/month rate of the end of the prophylactic treatment phase in GENA-04 was 54% lower compared with the corresponding rate in GENA-09. This suggests that long-term prophylactic treatment with simoctocog alfa is efficacious in patients with severe haemophilia, including those with severe joint damage.

The overall efficacy of prophylactic treatment with simoctocog alfa was based on the objective criteria of the monthly BE rate. The sponsor comments that this is a more stringent criteria than subjective criteria based on an individual investigator's assessment of his or her patient. In all four studies, a substantial majority of patients achieved excellent efficacy ratings (BE < 0.75) for all BEs and for spontaneous BEs. The efficacy ratings for the three clinical studies with data for **all** BEs at the end of the study are summarised below in Table 39.

Table 39: Efficacy of prophylactic treatment for ALL BEs.

Monthly BE rate	GENA-08 (n=32)	GENA-03 (n=59)	GENA-09 (n=22)
Excellent (< 0.75)	29 (90.6%)	49 (83.1%)	18 (81.8%)
Good (0.75 - 1.0)	2 (6.3%)	5 (8.5%)	1 (4.5%)
Moderate (>1.0 - 1.5)	1 (3.1%)	3 (5.1%)	2 (9.1%)
Poor (>1.5)	-	2 (3.4%)	1 (4.5%)

The efficacy ratings for the four clinical studies for **spontaneous** BEs at the end of the study are summarised below in Table 40.

Table 40: Efficacy of prophylactic treatment for SPONTANEOUS BEs*.

Monthly BE rate	GENA-08 (n=32)	GENA-03 (n=59)	GENA-09 (n=22)	GENA-04 (n=18) *
Excellent (< 0.75)	32 (100.0%)	56 (94.9%)	18 (81.8%)	17 (94.9%)
Good (0.75 - 1.0)	-	1 (1.7%)	2 (9.1%)	1 (5.8%)
Moderate (>1.0 - 1.5)	-	2 (3.4%)	2 (9.1%)	-
Poor (>1.5)	-	-	-	-

* All these patients also participated in GENA-09, and data relate to spontaneous bleeds only for this study).

The dose of simoctocog alfa for routine prophylaxis was 30 to 40 IU/kg for both children and adults in the two pivotal studies (GENA-08, GENA-03), and was administered every second day in adults and children with the option to administer the product three times a week in children. However, the sponsor is proposing a lower dose for prophylaxis of 20 to 40 IU/kg at intervals of

2 to 3 days for both children and adults (*Dosage and Administration,* PI). The sponsor comments that shorter dosage intervals or higher doses may be necessary in some patients, "especially in younger patients". In addition, the sponsor advises that FVIII levels should be determined during the course of treatment to guide the dose to be administered and the frequency of repeated infusions. It is unclear why the sponsor is proposing a dose for prophylaxis that differs from that used in the pivotal studies. The mean dose used in adults for prophylaxis in GENA-08 was 32.8 IU/kg (range: 24.0, 39.3), and the mean dose used in children for prophylaxis in GENA-03 was 38.9 IU/kg (range: 26.0, 56.7). The sponsor will be asked to comment on this matter in the s31 response to the questions arising from the first round evaluation of the submission. *See Section 11.1.3.7.*

6.5.2. On-demand treatment for BEs

The efficacy of on-demand treatment with simoctocog alfa was assessed in the three pivotal studies (GENA-01, GENA-08 and GENA-03) and in the two supportive studies (GENA-09 and GENA-04). A total of 135 patients across the five studies received on-demand treatment of BEs with simoctocog alfa. The majority of the 135 patients were from the three pivotal studies (83.7% [n=113]) with the remainder coming from the two supportive studies (16.3% [n=22]). The number of BEs across the five studies was 1208, with the majority coming from GENA-01 (81.6% [n=986]), which was specifically designed to assess the on-demand efficacy of simoctocog alfa. However, patients in GENA-01 did not receive routine prophylaxis aimed to prevent BEs. The number of infusions and the dose per infusion used to treat BEs across the five studies are summarised below in Table 41.

Table 41: Summary of BEs requiring on-demand treatment with simoctocog alfa.

Parameter	GENA-01 (n=22)	GENA-08 (n=32)	GENA-03 (n=59)	GENA-09 (n=22)	GENA-04 (n=18)
Number of treated BEs	986	30	108	47	37
Patients with treated BE (n)	22	15	32	14	8
Number of infusions (median)	1.0 (range: 1, 13)	1.0 (range: 1, 12)	1.0 (range: 1, 22)	1.5 (range: 1, 6)	1.0 (range: 1, 12)
Mean dose per infusion (IU/kg) Dose range /infusion (IU/kg)	32.3 ± 10.6 (7, 61)	33.3 ± 6.7 (20, 53)	45.1 ± 12.6 (25, 88)	32.6 ± 5.9 (8, 50)	34.6 ± 5.4 (24, 44)

Note: Number of infusions = median (range); Dose per infusion = mean ± SD; n = number of patients in the study and all patients in GENA-04 had been previously in GENA-09.

The mean dose per infusion was comparable across the four adult studies, but the median number of infusions in GENA-09 was 50% higher than in the three other studies. The mean dose per infusion in the paediatric study (GENA-03) was 30% to 40% higher than the mean dose per infusion across the four adult studies. Furthermore, the IVR (CHR assay) was approximately 24% lower in children than in adults based on the results from the paediatric study GENA-03

and the adult study GENA-01 (that is, IVR = 1.9% vs 2.5% per IU/kg, respectively). Therefore, the higher dose per infusion used to treat breakthrough BEs in children aged 2 to 12 years compared with adults might be due to lower FVIII recovery following simoctocog alfa in children than in adults. However, the sponsor comments that exact dosing was complicated in the paediatric study due to simoctocog alfa for this study being supplied exclusively in vials containing 500 IU and typically the entire contents of vials were infused for practical reasons. The sponsor states that a hypothetical patient with the mean body weight observed in the study of 27.3 kg would require a dose of 546 to 819 IU (20 to 30 IU/kg) for minor BEs according to the dosing recommendations, but 1000 IU (that is, 2 vials; 36.6 IU/kg) were probably infused because investigators may have preferred to infuse more rather than less FVIII in these paediatric patients. However, no data could be identified in the submission supporting the suggestion that investigators in study GENA-03 administered more than the recommended doses to children in the circumstances described by the sponsor.

The proportion of BEs requiring only 1 or 2 infusions was 96.8% in GENA-01, 88.9% in GENA-08 and 81.3% in GENA-03. For GENA-09, only data on the number of treatment days per BE were available, and the proportion of BEs requiring only 1 or 2 treatment days was 68.1%. The sponsor comments that the lower proportion of patients in GENA-09 requiring 1 or 2 infusions compared with GENA-01 and GENA-03, "is very likely to be explained by the severe baseline condition of the patients enrolled in GENA-09 and the high proportion of moderate to major BEs observed in this study".

The overall efficacy results for treatment of breakthrough BEs for any, minor, and moderate to major BEs for the five studies are summarised below in Table 42. The table does not include data for major to life-threatening BEs, as the 5 studies included only 3 BEs in this category. The 3 major to life-threatening BEs all occurred in GENA-01, and treatments were rated as good for 2 of these bleeds and moderate for 1 of the bleeds. Overall, the highest efficacy was observed in GENA-08, with 100% of available efficacy assessments for the total number of BEs being excellent or good. The lowest overall proportion of successful treatments was seen in GENA-09 with 61.7% of the total number of BEs with available efficacy assessments being rated as excellent or good. Across all studies, efficacy was higher for minor than for moderate to major BEs and nearly all treatments for minor BEs across the five studies were rated as excellent or good. The percentage of children with moderate to major BEs reporting excellent or good efficacy was notably lower than the percentage of adults from GENA-01 and GENA-08 reporting excellent or good efficacy.

Table 42: Efficacy assessment for treatment of BEs with available data according to severity of the BE (any, minor, moderate to major).

Efficacy rating	GENA-01	GENA-08	GENA-03	GENA-09	GENA-04
Any BE	986	28	108	47	37
Excellent	60.3%	71.4%	71.3%	29.8%	37.9%
Good Moderate	34.1% 5.5%	28.6% -	11.1% 15.7%	31.9% 38.3%	45.9% 8.1%
None	-	-	1.9%	-	
Minor BE	416	14	61	17	20
Excellent	75.0%	85.7%	86.9%	58.8%	70.0%

Efficacy rating	GENA-01	GENA-08	GENA-03	GENA-09	GENA-04
Good	23.6%	14.3%	11.5%	35.3%	30.0%
Moderate	1.4%	-	1.6%	5.9%	-
None	-	-	-	-	-
Moderate - Major BE	566	14	46	30	17
Excellent	50.0%	57.1%	50.0%	13.3%	-
Good	41.7%	42.9%	10.9%	30.0%	64.7%
Moderate	8.3%	-	34.8%	56.7%	17.6%
None	-	-	4.3%		17.6%

The on-demand doses for the treatment of BEs in the three pivotal studies (GENA-01, GENA-08, GENA-03) were higher than the doses being proposed by the sponsor in the *Dosage and Administration* section of the PI (see Table 43 below). However, the sponsor states that taking into consideration that almost 50% of the BEs were moderate to major and that nearly 50% of the surgeries were major, the average actual doses administered are in line with proposed doses. The mean dose per infusion for the treatment of on-demand BEs ranged across the three pivotal studies from 32 IU/kg to 45 IU/kg, and the administered doses ranged from 7 to 88 IU/kg. In the 5 studies, the highest mean dose was reported in children (45 IU/kg), and the highest dose across the three studies was administered to a child (88 IU/kg).

Table 43: Proposed dose (based on the PI) for on-demand BEs and the administered dosing recommendations from the five clinical studies.

Severity BE	Proposed Dose - based on PI	GENA-01, -08, -03, -04	GENA-09
Minor	FVIII required levels 20-40%; repeat every 12–24 h. At least 1 day, until the BE, as indicated by pain is resolved or healing is achieved. *(Recommended dose is not stated in the PI but would be 10-20 IU/kg based on the required FVIII levels).*	FVIII peak levels 40-60%; dose 20-30 IU/kg every 12-24 hr until BE resolution.	FVIII peak levels 40-60%; dose 10-20 IU/kg every 12-24 hr until BE resolution.
Moderate to Major	FVIII required levels 30-60%; repeat every 3 to 4 days of more until pain and	FVIII peak levels 60-80%; dose 30-40 IU/kg every 12-24 h	FVIII peak levels 40-60%; dose 15-30 IU/kg every 12-24 hr until BE

Severity BE	Proposed Dose - based on PI	GENA-01, -08, -03, -04	GENA-09
	acute disability are resolved. *(Recommended dose is not stated in the PI but would be 15-30 IU/kg based on the required FVIII levels).*	until BE resolution.	resolution.
Major to life-threatening	FVIII required levels 60-100%; dose 30-50 IU/kg, repeat every 8-12 hr until threat is resolved. *(Recommended dose is not stated in the PI but would be 30-50 IU/kg based on the required FVIII levels).*	FVIII peak levels 100-120%; initial dose 50-60 IU/kg and subsequently 20-25 IU/kg every 8-12 h until BE resolution.	FVIII peak levels 100-120%; initial dose every 8-12 hr and subsequently a dose of 20-25 IU/kg until BE resolution.

The sponsor states that "the amount and frequency of administration should always be orientated the clinical effectiveness in the individual case" and that this is outlined in the European SPC. (The information in the SmPC is the same as that provided in the PI). Furthermore, the sponsor states that calculation of simoctocog alfa dosage required for prophylaxis or treatment of bleeding in each of the clinical studies was based on the assumption that 1 IU FVIII/kg would raise the plasma FVIII activity by 1.5% to 2% of normal, and that the dosing scheme for on-demand treatment was validated by the results obtained for incremental recovery of FVIII in each of the studies. The results for IVR for the three pivotal efficacy studies for actual doses of simoctocog alfa as determined by the CHR and OS assays are summarised below in Table 44. The data show that the IVR was notably lower in children (GENA-03) than in adults (GENA-01, GENA-08).

Table 44: Summary of recovery (IVR) for the three pivotal studies, doses are actual doses received as determined by the CHR and OS assays.

n			IVR Start		IVR 3 months		IVR 6 months	
			Dose IU/kg	IVR % per IU/kg	Dose IU/kg	IVR % per IU/kg	Dose IU/kg	IVR % per IU/kg
GENA-01	20-22[1]	CHR	58.7 ± 3.7	2.50 ± 0.37	59.0 ± 5.2	2.44± 0.56	58.7 ± 4.8	2.34 ± 0.50
		OS	48.6 ± 3.3	2.14 ± 0.27	50.3 ± 4.2	2.06 ± 0.39	50.0 ± 4.0	2.01 ± 0.33

n			IVR Start		IVR 3 months		IVR 6 months	
GENA-08	30 - 32 [2]	CHR	55.6 ± 2.8	2.57 ± 0.54	53.5 ± 4.6	2.37 ± 0.50	53.6 ± 2.3	2.34 ± 0.40
		OS	47.8 ± 2.8	2.20 ± 0.47	45.1 ± 4.2	2.05 ± 0.35	45.3 ± 2.5	2.01 ± 0.30
GENA-03	26 - 55 [3]	CHR	53.1 ± 1.5	1.83 ± 0.41 [4]	52.2 ± 4.3	1.70 ± 0.40	51.6 ± 3.1	1.77 ± 0.46
		OS	45.1 ± 1.1	1.58 ± 0.33 [4]	44.4 ± 4.0	1.47 ± 0.36	43.9 ± 2.7	1.53 ± 0.34
		CHR	52.7 ± 2.9	1.57 ± 0.51 [5]				
		OS	45.0 ± 2.7	1.42 ± 0.36 [5]				

1 = GENA-01, n=20 at month 3. 2 = GENA-08, n=32 at start, n=31 at 3 months, n=30 at 6 months 3 = GENA-03, n=26 at start Phase I, n=31 at Phase II start, n=55 at 3 months; n=53 at 6 months. 4 = The results for IVR start are those for Phase I of the study. 5 = The results for IVR start are those for Phase II of the study.

Despite the sponsor's justification for the proposed dosage regimen for on-demand treatment of BEs it remains unclear why the proposed dosage regimen should differ from that used in 4 of the 5 clinical studies (including the 3 pivotal studies). The sponsor will be asked to comment on this matter in the s31 response to the questions arising from the first round evaluation of the submission. *See Section 11.1.3.6.*

6.5.3. Surgical prophylaxis

In the five studies, the efficacy of simoctocog alfa for surgical prophylaxis was assessed in a total of 33 surgical procedures in 19 patients, with 20 procedures in 7 patients being classed as minor and 13 procedures in 12 patients being classed as major. For surgical procedures, simoctocog alfa mean dose ranged from 35.0 IU/kg per infusion in GENA-09 to 50.2 IU/kg per infusion in GENA-01. The overall number of infusions administered ranged from 1 to 5 for minor surgical procedures and from 4 to 35 for major surgical procedures. For all surgical procedures, actual blood loss was no higher than the maximum expected blood loss. Intra-operative simoctocog alfa was required for only one patient undergoing major surgery (TKR in GENA-04). Blood transfusions/FFP were administered on 3 occasions to 2 patients in GENA-04 undergoing major surgery (1xTHR and 1x revision in 1 patient; 1xTKR in 1 patient), and treatment with anti-fibrinolytics was given to 1 patient undergoing joint replacement surgery in GENA-08 and 1 patient undergoing circumcision in GENA-03. Post-operative wound haematoma was reported in only 1 patient (GENA-03), and this patient was subsequently diagnosed with VWD.

The overall efficacy of simoctocog alfa for surgical procedures was evaluated intra-operatively and post-operatively, following the final suture of the surgical incision until at least 2 days (minor surgery) or at least 6 days (major surgery) after surgery or until healing was complete. Efficacy criteria included the amount of blood loss (compared to expected) and the need for additional infusions not originally anticipated for the type of procedure. For all surgical procedures combined (that is, minor and major), efficacy was rated as excellent for 87.9% (29/33), good for 9.1% (3/33), moderate for 3.0% (1/33), and none for 0% (0/33). For the 20 minor surgical procedures, efficacy was rated as excellent for all procedures. For the 13 major surgical procedures efficacy was rated as excellent for 69.2% (9/13), good for 23.1% (3/13), and moderate for 7.6% (1/13).

The proposed dose (based on the PI) and the recommended dose used in all studies for surgical prophylaxis are summarised below in Table 45. It is unclear why the proposed dosage regimens differ from those used in all 5 clinical studies. In particular, no pre-operative dose is being proposed for minor surgical procedures (including tooth extraction) although this was recommended in all studies. The sponsor will be asked to comment on this matter in the s31 response to the questions arising from the first round evaluation of the submission. *See Section 11.1.3.7.*

Table 45: Proposed dose (based on PI) and the recommended dose for surgical prophylaxis used in all 5 clinical studies.

Procedures	Proposed Dose - based on PI	All studies - GENA-01, -08, -03, -09, -04,
Minor including tooth extraction	FVIII level required 30-60%; (15-30 IU/kg) every 24 hours at least 1 day until healing is achieved. *(Recommended dose is not stated in the PI but would be 15-30 IU/kg based on the required FVIII levels).*	25–30 IU FVIII/kg within 3 h prior to surgery to achieve peak target level of approximately 50–60%, repeated every 12–24 h until healing is complete. Trough level maintained at approximately 30%.
Major	FVIII level 80-100% (pre- and post-operatively); repeat infusion every 8-12 hours until adequate wound healing, then therapy for at least another 7 days to maintain a FVIII level of 30 to 60%. *(Recommended dose is not stated in the PI but would be 40-50 IU/kg initially and 15-30 IU/kg subsequently based on the required FVIII levels).*	50 IU FVIII/kg within 3 h prior to surgery to achieve target peak level of approximately 100%, repeated if necessary after 6–12 h initially and for ≥ 6 days until healing is complete. Trough level maintained at approximately 50%.

7. Clinical safety

7.1. Studies with clinical safety data

All five completed studies included safety data on simoctocog alfa for the treatment of severe haemophilia A. The submission included an integrated summary of the safety data from the five clinical studies. In this CER, the evaluation of safety includes a review of the integrated safety

data, supplemented where relevant from the individual study reports, and a separate review of the safety data from the paediatric study GENA-03.

7.2. Integrated safety summary (total safety population)

7.2.1. Extent of exposure

A total of 135 individual patients underwent treatment with simoctocog alfa in the four completed studies and are included in the safety population (GENA-01, GENA-08, GENA-03, GENA-09), and 18 of the patients from GENA-09 continued into the long-term extension study GENA-04. The exposure data for the safety populations from the five completed studies are summarised below in Table 46.

Table 46: Study drug exposure data (mean and range); safety populations.

Parameter	GENA-01	GENA-08	GENA-03	GENA-09	GENA-04*
Number of patients	22	32	59	22	18
Number of EDs/patient	53.3 18–97	90.3 17–105	96.1 24–152	97.7 79–132	226 14–299
Number of infusions/patient	54.9 18–115	91.3 17–113	97.4 26–152	97.9 79–132	228 14–319
Total dose, IU	135,947 68,395–279,150	248,516 61,545–389,728	104,813 24,005–374,225	226,576 143,500–371,250	585,489 34,000–996,550
Total dose, IU/kg	1835 768–3443	3062 555–3949	3829 1050–7180	3253 2670–4474	6289 4825–8629
Duration of study (days)	342.7 205–674	179.9 39–218	208.6 49–338	201.8 191–241	455.6 33–563

* The 18 patients in GENA-04 also participated in GENA-09.

Adverse events (AEs) were defined as untoward medical occurrences not necessarily having a causal relationship with treatment. The outcomes were documented for each AE. *Adverse drug reactions (ADRs)* included AEs for which a causal relationship was at least possible. The potential causal ratings were probable, possible, unlikely, unrelated, and unclassified. *Serious AEs (SAEs)* were any untoward medical occurrence resulting in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is another important medical event. Hospitalisation was not considered a SAE in cases where the hospitalisation took place because of study related procedure (for example, PK assessment) or was a scheduled surgical procedure planned prior to study enrolment.

ADRs were classified by the sponsor as expected (listed in the Investigator's Brochure) or unexpected. *Significant AEs* were any marked laboratory abnormalities or any AEs that led to an intervention, including withdrawal of drug treatment, dose reduction or significant additional concomitant therapy. *Severity of AEs* was categorised as mild, moderate, or severe based on limitations of activity and extent of medical intervention required for treatment. *AEs requiring therapy* were to be treated with recognised standards of medical care to protect the health and well-being of the subject.

The condition of the patients was monitored throughout the study. At each scheduled or unscheduled study visit, AEs were documented by the investigator and patient diaries were checked for any documented event. At each visit the patient was asked to answer "Yes" or "No" to the question, "Did you experience any problems since the last visit/during the previous study period?" Any AE or ADR occurring during the study was noted in detail on the appropriate pages of the CRF. If a patient reported several signs or symptoms, representing a single syndrome or diagnosis, the latter was to be recorded in the CRF. The responsible investigator graded the severity of all AEs or ADRs (mild, moderate or severe) and their seriousness (non-serious or serious) according to pre-defined criteria specified in the study protocols. The sponsor was responsible for assessing whether each ADR was expected or unexpected as

defined in the protocols. In the event of clinically relevant abnormal laboratory findings, the tests were to be repeated and followed up until they returned to normal and/or an adequate explanation was available.

Diseases, signs and symptoms and/or laboratory abnormalities already existing before the first administration of study medication were not considered as AEs when observed at a later stage, unless they represented an exacerbation in intensity or frequency (worsening).

The responsible investigator was accountable for providing detailed information concerning any abnormalities and the nature of, and reasons for any necessary actions, as well as any other observations or comments which were useful for the interpretation and understanding of the AEs or ADRs.

Comment: The relevant definitions for adverse events were standard for clinical trials of the type included in the submission. All adverse events were treatment-emergent. No time interval for collection of AEs could be identified (for example, up to an including 30 days).

7.3. Adverse events

7.3.1. Overall adverse event profile

The overall adverse event profiles of the five studies are summarised below in Table 47.

Table 47: Simoctocog alfa adverse event profiles in the five studies; safety populations.

Study	No. of pts in study	No. (%) of pts with AEs	No. of AEs	No. (%) of pts with SAEs	No. of SAEs	No. pts with severe AEs	Possibly or probably related AEs
GENA-01	22	12 (54.5)	69	2 (9.1)	3	3	0
GENA-08	32	21 (65.6)	65	2 (6.3)	2	4	5
GENA-03	59	38 (64.4)	124	5 (8.5)	7	0	2†
GENA-09	22	6 (27.3)	9	0 (0)	0	0	0
GENA-04	18	2 (11.1)	5	0 (0)	0	0	1
Total	135‡	79 (58.5)	272	9 (6.7)	12	7	8

† AEs rated as possibly related; 6 more AEs in 3 patients were rated as unlikely to be related. ‡ The 18 patients in GENA-04 also participated in GENA-09. AE = adverse event; SAE = serious adverse event.

7.3.2. Adverse events (irrespective of relationship to treatment)

A total of 272 treatment-emergent AEs were reported in 58.5% (79/135) of patients in the total safety population. The most commonly occurring AEs (systems, organ, class [SOC]) reported in the total safety population (n=135) with an incidence of ≥ 5% in descending order of frequency were "infections and infestations" (40.7%, n=55), "gastrointestinal disorders" (18.5%, n=25), "general disorders and administration site conditions" (18.5%, n=25), "injury poisoning and procedural complication" (18.5%, n=25), "musculoskeletal and connective tissue disorders" (14.1%, n=19), "respiratory, thoracic, and mediastinal disorders" (13.3%, n=18), "investigations" (11.1%, n=15), and "skin and subcutaneous disorders" (n=9, 6.7%). The majority of "infections and infestations" occurred in the paediatric study GENA-03, which is not unexpected.

Treatment-emergent AEs (preferred term) occurring in ≥ 5% of patients in descending order of frequency in the total safety population were nasopharyngitis (8.1%), pyrexia (7.4%), headache (7.4%), and rhinitis (5.2%). In the SOC of "immune system disorders" there was 1 case of allergic oedema in a paediatric patient in GENA-03, and 1 case of seasonal allergy in an adult patient in GENA-09. There were no hypersensitivity reactions in the total safety population.

There were no thromboembolic events in the total safety population. The AEs (preferred term) occurring in ≥ 2% of patients in the total safety population are summarised below in Table 48.

Table 48: Treatment-emergent AEs (preferred term) occurring in ≥ 2% of patients in the total safety population.

Preferred term AEs	n	%
Number of patients	135	
Number of patients with AEs	79	58.5%
Nasopharyngitis	11	8.1%
Pyrexia	10	7.4%
Headache	10	7.4%
Rhinitis	7	5.2%
Cough	6	4.4%
Diarrhoea	5	3.7%
Chills	5	3.7%
Injury	5	3.7%
Rash	5	3.7%
Abdominal pain	4	3.0%
Varicella	4	3.0%
Arthralgia	4	3.0%
Back pain	4	3.0%
Bronchitis	3	2.2%
Upper RTI	3	2.2%
Head injury	3	2.2%

7.3.3. Treatment-related adverse events (adverse drug reactions)

Of the total number of patients in the safety population, 5 (3.7%) patients experienced 8 AEs classified by the investigators as possibly or probably related to treatment (see Table 49, below).

Table 49: Treatment-emergent AEs classified as possibly or probably related to treatment; safety population. [Patient information has been redacted from this table]

Study	Preferred term (MedDRA)	Intensity	Outcome	Causality
GENA-08	Injection site pain	Mild	Recovered/Resolved	Possible
	Vertigo	Mild	Recovered/Resolved	Possible
	Dry mouth	Mild	Recovered/Resolved	Possible
	Paraesthesia	Mild	Recovered/Resolved	Possible
	Injection site inflammation	Mild	Recovered/Resolved	Possible
GENA-03	Back pain	Mild	Recovered/Resolved	Possible
	Headache	Mild	Recovered/Resolved	Possible
GENA-04	Anti-FVIII antibody positive	Mild	Unknown	Probable

During the final IDMC meeting for GENA-03 (paediatric study) conducted after the database lock, the committee commented that a further 6 AEs could be judged as "possibly related" since they occurred temporally associated with the respective last infusion of simoctocog alfa. These 6 AEs had all been judged by investigators to be unrelated to treatment. The 6 AEs included 3 cases of mild rash and 3 cases of chills (1 mild and 2 moderate in severity), all of which resolved without sequelae. Review of these additional AEs indicates that 3 patients each experienced 1 AE of chills, 1 patient experienced 2 AEs of rash on two separate occasions, and 1 patient experienced an AE of rash. There were no inconsistencies between investigator and IDMC safety assessments in studies GENA-01, GENA-08, GENA-09 or GENA-04. In total, there were 10 (7.4%) patients in the total safety population with 14 AEs (5.1%) judged by the investigator and/or IDMC to be possibly or probable related to simoctocog alfa.

7.3.4. Deaths and other serious adverse events (SAEs)

7.3.4.1. Deaths

One death occurred in GENA-08 and was deemed not related to administration of simoctocog alfa. This patient had been diagnosed with epilepsy and had been taking an antiepileptic (oxycarbazepin, 300 mg twice a day) since 1997. The last documented simoctocog alfa infusion according to the patient diary was 48 days before his death. The patient experienced status epilepticus, and the CRF stated acute respiratory and cardiovascular failure as the cause of death.

7.3.4.2. Other serious adverse events (SAEs)

There were 11 other SAEs in 8 (5.9%) patients in the 5 studies: 3 SAEs (in 2 patients) in GENA-01, 7 SAEs (in 5 patients) in GENA-03 and 1 SAE (in 1 patient) in GENA-08. The SAEs (preferred term) reported in the total safety populations are summarised below in Table 50.

Table 50: SAEs; safety population. [Patient information has been redacted from this table]

Study		Outcome	Causality	Comment
GENA-01	Depression, suicidal	Recovered/Resolved	Not related	H/o depression.
	Hepatic encephalopathy	Recovered/Resolved	Not related	H/o hepatitis C and chronic liver disease.
	Hepatic cirrhosis	Not recovered/Not resolved	Not related	
GENA-08	Traumatic fracture	Recovered/Resolved	Not related	
GENA-03	Device-related infection	Recovered/Resolved	Not related	Port catheter infection.
	Head injury	Recovered/Resolved	Not related	
	Head injury	Recovered/Resolved	Not related	
	Acute tonsillitis	Recovered/Resolved	Not related	All three events occurred simultaneously.
	Upper RTI	Recovered/Resolved	Not related	
	Lower RTI	Recovered/Resolved	Not related	
	Haemarthrosis	Recovered/Resolved	Not related	

7.3.5. Discontinuation due to adverse events

Treatment discontinuations for all reasons are summarised below in Table 51. The only AEs resulting in treatment discontinuation were those related to one death reported in GENA-08.

Table 51: Patient withdrawals by study.

Study	Age at entry	EDs completed (n)	Reasons for withdrawal
GENA-01	28	24	Subject lost to withdrawal
GENA-08	38	17	Consent withdrawn
	26	76	Status epilepticus; acute respiratory and cardiovascular failure
GENA-03	9	42	Therapy failure
	7	24	Protocol violation - von Willebrand disease newly diagnosed
GENA-04	36	14	Consent withdrawn
	19	117	Consent withdrawn

7.4. Laboratory tests

7.4.1. Immunogenicity

No FVIII inhibitors had been detected up to April 2013. The threshold definitions were ≥0.6 to <5 BU for a "low titre" inhibitor, and ≥ 5 BU for a "high-titre" inhibitor.

Non-inhibitory anti-rhFVIII antibodies were detected in 4 patients (1 patient in GENA-01, 2 patients in GENA-03 and 1 patient in GENA-04).

FVIII inhibitory and non-inhibitory antibodies were measured by validated methods in a central laboratory. Inhibitory antibodies were measured by the modified Nijmegen method, as suggested by the current FVIII EMEA guideline (EMEA/CHMP/BPWP/144533/2009), preferably when FVIII plasma concentrations had reached baseline. Besides the standard Nijmegen assay (using normal human plasma as test base), an additional Nijmegen assay was performed using FVIII-depleted human plasma spiked with simoctocog alfa (1 IU/mL) as test base. A special ELISA-based test was developed by the central laboratory for detecting non-inhibitory antibodies against simoctocog alfa. Repeated immunogenicity testing for both FVIII inhibitory and non-inhibitory antibodies was undertaken throughout the course of each of the five clinical studies.

Abbreviated case narratives for the four patients in the total safety population with non-inhibitory anti-rhFVIII antibodies are provided below.

- In GENA-01, one patient had a low-titre (titre 0.15) non-inhibitory anti-FVIII antibody that was already present at screening. The antibody was also detected pre-injection during PK Cycle 1 (titre not specified), and pre-injection (titre 0.26) and 48 hours post-injection (titre 0.27) during PK Cycle 2. However, it was not detected after 10 to 15 EDs, at 3 months and at the completion visit.
- In GENA-03, non-inhibitory antibodies against FVIII were detected in 2 patients. One patient had a non-inhibitory antibody against FVIII, which was detected in all

measurements throughout the study from screening (titre 1.42) to the 6-months visit (titre 0.99). The highest titre was detected 48 hours after infusion in PK Cycle 1 (titre 1.48) and the lowest titre was detected at 6 months (titre 0.99). This patient received simoctocog alfa for routine prophylaxis and efficacy was rated as excellent at the end of the study period, and for surgical prophylaxis for a planned major surgery and efficacy was rated excellent both intra-operatively and overall. In one patient, a non-inhibitory antibody titre of 0.632 was detected at screening, but not in any subsequent visit up to 6 months. In this patient the efficacy of routine prophylaxis was rated as excellent at the end of the study period.

- In GENA-04, one patient who was negative at baseline tested positive for non-inhibitory antibody at one time point (completion visit). The positive sample was tested by the central laboratory at 8 dilutions (1, 3, 9, 27, 81, 243, 729 and 2187). The result was positive only at dilution factor 1 and the antibody titre was very low (titre 0.34). Simoctocog alfa efficacy in this patient did not appear to be affected.

7.4.2. Other laboratory tests (haematology, biochemistry, urinalysis)

- **GENA-01**

In GENA-01, safety laboratory tests (haematology and biochemistry) and urinalysis were performed at screening, during PK cycle 1 and 2 pre-infusion and 48 hours post-infusion, at 3-months pre-infusion, at 6-months pre-infusion and post-infusion at 24 hours (haematology and biochemistry only) and 48 hours, and at the completion visit. Safety laboratory testing was also undertaken in association with surgical procedures.

Three patients had abnormal, clinically significant laboratory or urinalysis values and these are summarised below:

- One patient had increased protein in urine during PK Cycle 2 (with full-length rFVIII) and at the 6-month and completion visits, and increased glucose in urine pre-injection during PK Cycle 1 and from PK Cycle 2 to completion. He also had increased ketone values at 6 months. Glucose in urine during PK Cycle 1, protein in urine during PK Cycle 2 and protein and ketones in urine at the 6-month visit were also reported as AEs. This patient had a known history of type 2 diabetes mellitus. Consequently, it is likely that this pre-existing medical condition accounted for the abnormal laboratory findings.
- One patient, who had a surgery for TKR, had several haematology and clinical chemistry abnormalities in the post-operative period, including low red blood cell count, haemoglobin and haematocrit; increased ALT, AST, bilirubin and LDH; and abnormal glucose level in urine at pre-injection PK Cycle 1 (with full-length rFVIII). Apart from glucose in the urine, all were also reported as AEs. The ALT and AST levels were not followed after the patient's last surgical visit on post-operative Day 7. However, at the completion visit the ALT and AST levels were not considered to be abnormal or clinically significant. This patient had a history of type 2 diabetes mellitus, HCV and HIV infections, hypertension and haemophilic arthritis. Consequently, it is likely that these pre-existing medical conditions accounted for the abnormal laboratory findings.
- One patient had abnormal protein in the urine at screening and again at the 3-months visit. No information was provided for this patient. However, given that the abnormality was reported at screening and then only at the 3-months visit it is unlikely to be clinically significant.

- **GENA-03**

In GENA-03, safety laboratory tests (haematology and biochemistry) were performed at screening, Phase 1 (Cycles 1 and 2) before and 24 and 48 hours after the end of the infusion, Phase II (baseline) before and 48 hours after the end of the infusion, Phase II (3-month visit)

pre-infusion, and Phase II (6-month visit) pre-infusion. Urinalysis was not performed in this study.

Three patients had a total of 30 haematological abnormalities that were rated as clinically significant. All three patients had a history of iron deficiency anaemia/anaemia and no AEs relating to these conditions were noted for any of the three patients. The laboratory abnormalities are in the three patients are summarised below:

- One patient (1 abnormality) had an abnormally low haematocrit before simoctocog alfa administration at his 6-months visit. However, the haematocrit had also been low 48 hours after ED 1 and at 3 months and even lower before that, but these values had not been rated as clinically significant abnormalities
- One patient (21 abnormalities) had an abnormally low erythrocyte count at screening, before and 24 hours after infusion for PK Cycle 2 and at 6 months.
- One patient (8 abnormalities) had abnormally low haemoglobin and haematocrit levels at screening, at recovery 1, 48 hours after ED 1 and at 3 months, but not at 6 months

- **GENA-09**

In GENA-09, safety laboratory tests (haematology) and urinalysis were performed at screening, Cycle 1 and Cycle 2 before and 24 and 48 hours after the end of the infusion, baseline at the 3-month visit and the 6-month visit. One patient had a bacterial infection on urinalysis at screening and this persisted throughout the study. Urinalysis also showed clinically abnormal erythrocytes during PK Cycle 2 at 48 hours after administration of simoctocog alfa and at the 6-month visit before administration, and elevated nitrites during both PK cycles. Leucocytes remained clinically significant during the PK cycles and at the 6-month PK visit. Worsening of leukocyturia and haematuria were recorded as AEs during the PK phase of the study for this patient.

- **GENA-04 and GENA-08**

No significant laboratory abnormalities were reported in GENA-04 or GENA-08. In GENA-04, safety laboratory tests were performed at first recovery visit, at 3 months and at the study completion visit. In GENA-08, safety laboratory tests were performed at screening, at the first visit and at 3 month and 6 month visits. In both studies safety laboratory tests were performed before and after surgeries.

7.4.3. Viral safety

Simoctocog alfa is produced in human cell lines. The sponsor states that numerous assays have been used on the cells used in production of simoctocog alfa for the detection of possible endogenous and infectious viruses or mycoplasma. Since the cell line is of human origin, additional specific tests for human viruses and for bovine, murine and porcine viruses have been performed, without any evidence of their presence. In addition, the purification process includes two specific steps for virus inactivation/removal.

During the clinical studies, if abnormal ALT or AST values persisted for more than one week, viral serology and polymerase chain reaction (PCR) testing was to be performed to rule out HBV and HCV infection. In addition, PCR testing of the corresponding investigational medicinal product (IMP) batches was to be performed. The sponsor stated that no patients have been found to be positive for these viruses in any studies so far.

7.5. Vital signs

Vital signs (heart rate, systolic and diastolic blood pressure and body temperature) were examined in all studies. No routine electrocardiographic (ECG) assessments appear to have been undertaken.

In GENA-01, vital signs were examined at screening, at both PK assessments, at 3- and 6-months, at completion visit (if different from the 6 month visit), and before and after surgical procedures. A total of 8 patients had at least one abnormal finding at screening, and abnormalities were seen in 7 patients at the completion visit. Several abnormalities detected on physical examination were considered to be a consequence of haemophilia A (for example, haemophilia arthropathy, joint swelling, ecchymosis at the site of a BE), or to be due to underlying conditions or previous procedures (for example, stasis dermatitis and liver edge palpable in a patient with type 2 diabetes mellitus and HCV infection; knee incision scar and iron staining in the patient who had right total knee revision; healed scar and thin build, respectively, in another 2 patients). None of the observed vital sign abnormalities were rated as AEs. Shift tables demonstrated that most abnormalities seen at the completion visit had been present at baseline, with the exception of one patient who was notably lighter at the completion visit than at the screening visit (59.6 kg vs 64.3 kg, respectively).

In GENA-08, vital sign examination was performed at screening, at the first visit, at 3- and 6-month visits, and before, during and after surgical procedures. One patient had high blood pressure at Visit 1 both before and 1 hour after the infusion (198/130 mmHg and 195/139 mmHg, respectively), which was rated as a clinically significant abnormality. However, blood pressure had been similarly elevated at screening (190/132 mmHg) but had not been judged clinically significant. Therefore, no AE of hypertension was recorded for this patient. No other vital signs were rated as clinically abnormal at any other time point for any other patient. Physical examination showed at least one abnormal finding in 12 patients at screening and in 9 patients at the 6-month visit. Apart from abnormalities that were likely to be a consequence of haemophilia A, 5 patients had skin abnormalities, 2 had abnormalities in ears, nose and throat, and 1 patient each had "palsy" and hypertension. None of the abnormalities observed were classed as AEs. Shift tables demonstrated that most abnormalities seen at 6 months had already been present at baseline, with the exception of two surgical procedures that had occurred during the study (1x knee arthropathy and 1x hip replacement). In one patient, a fixed flexion deformity was reported at 6 months that had not been documented at baseline, but this abnormality was described as long-standing by the investigator.

In GENA-03, vital signs were examined at screening, at both PK assessments for patients in the PK population and at baseline for patients only participating in the open phase, at 3 and 6 months, and before, during and after surgeries. No clinically relevant abnormalities in vital signs were observed. At least one abnormal finding was reported in 20 patients at screening and in 7 patients at the 6-month visit. Shift tables showed that physical examination abnormalities at the 6-month visit were reported for 5 patients for whom an abnormality was not reported at screening. These abnormalities were described as "other" in the relevant shift table, and no further information was provided. However, the sponsor commented that shifts in physical examination abnormalities from baseline to 6 months did not indicate any significant safety concerns.

In GENA-09, vital sign examination was performed at both PK visits, at 3- and 6-month visits and before, during and after surgical procedures. Physical examinations at baseline and 6 months (excluding abnormalities as a consequence of haemophilia A) were normal except for cardiovascular abnormalities in one patient (blood pressure 184/94 mmHg and systolic murmur in the cardiac apex and aorta at baseline, and arterial hypertension at 6 months). The cardiovascular abnormality was considered not to be an AE.

In GENA-04, vital sign analysis was performed at screening, at first recovery visit, at months, at the study completion visit, and before, during and after surgeries. One patient had arterial hypertension at screening only. This was considered not to be an AE.

7.6. GENA-03 (paediatric study)

7.6.1. Extent of exposure

Of the total number of 135 patients included in the safety population, 59 (43.7%) patients aged 2 to 12 years were from the paediatric study GENA-03. The paediatric safety population (n=59), received a total of 5746 infusions of simoctocog alfa. Of these infusions, 5316 (92.5%) were given for on-going prophylaxis, 216(3.8%) were for the treatment of BEs, 41 (0.7%) were for surgical prophylaxis, and 173 (3.0%) were for PK and recovery assessments. The extent of total exposure is summarised in below in Table 52.

Table 52: Extent of total exposure to simoctocog alfa; safety population (n=59).

Parameter	Mean	SD	Median	Range
Number of EDs	96.1	21.97	93.0	24–152
Number of infusions	97.4	22.31	95.0	26–152
Total dose, IU	104,812.9	60,258.98	96,270.0	24,005–374,225
Total dose, IU/kg	3828.9	1115.86	3700.3	1050–7180

7.6.2. Adverse events

7.6.2.1. Overview

A total of 124 treatment-emergent AEs were recorded in 38 of the 59 patients (64.4%), and are summarised below in Table 53.

Table 53: GENA-03 - Summary statistics for AEs; safety population (n=59).

Category*	N	%
AE	38	64.4
Probably or possibly related AE	2	3.4
SAE	5	8.5
Probably or possibly related SAE	0	0
Severe AE	0	0
Temporally related AE†	33	55.9
Death	0	0
Death due to probably or possibly related AE	0	0
AE leading to discontinuation of study drug	0	0
Probably or possibly related AE leading to discontinuation of study drug	0	0
SAE or AE leading to discontinuation of study drug	5	8.5

* Occurring in a patient at least once; † AEs beginning within 24 after infusion.
AE = adverse event; SAE = serious adverse event.

7.6.2.2. Adverse events (irrespective of relationship to treatment)

SOCs including more than 1 patient with an AE in descending order of frequency in the safety population were: "infections and infestations" (20/59, 33.9%); "injury, poisoning, procedural complications" (14/59, 23.7%); "general disorders and administration site conditions" (7/59, 11.9%); "respiratory, thoracic, and mediastinal disorders" (6/59, 10.2%); "skin and subcutaneous tissue disorders" (6/59, 10.2%); "musculoskeletal and connective tissue disorders" (5/59, 8.5%); and "nervous system disorders" (4/59, 6.8%).

Of the 124 AEs, 99 (79.8%) were mild and the remaining 25 (20.2%) were moderate, and no severe AEs were reported. AEs (preferred term) occurring in ≥ 1 patient in the safety population (n=59) in descending order of frequency were: nasopharyngitis (6, 10.2%); rhinitis (6, 10.2%); pyrexia (5, 8.5%); injury (5, 8.5%); cough (5, 8.5%); chills (4, 6.8%); headache (4, 6.8%); rash (4, 6.8%); varicella (3, 5.1%); head injury (3, 5.1%); bronchitis (2, 3.4%); ear infection (2, 3.4%); otitis media (2, 3.4%); pharyngitis (2, 3.4%); tonsillitis (2, 3.4%); upper RTI (2, 3.4%); joint injury (2, 3.4%); limb injury (2, 3.4%); arthralgia (2, 3.4%); back pain (2, 3.4%); and pain in extremity (2, 3.4%). Examination of the 39 AEs reported only once did not identify any unusual or unexpected events in the safety population. There was 1 case of allergic oedema. There were no hypersensitivity reactions. There were no thromboembolic events.

AEs typical of patients with haemophilia A (for example, haemarthrosis) were rare, which is in agreement with the relatively good joint status in the enrolled patients as evidenced by their HJHS. All AEs resolved without sequelae, except for 4 AEs occurring in 1 patient each that were classified as resolving/not resolved (1 x varicella, 1 x catheter pain, 1 x asthma, 1 x dry skin) and 1 AE of worsening of chronic cough that had been present at screening.

Thirty-three (33) patients experienced 78 AEs (62.9%) that occurred within 24 hours of 73 infusions (that is, temporally related). However, this finding was not unexpected as the prophylaxis schedule stipulated that infusions be administered every other day or 3 times a week. Therefore, all AEs had an approximately 50% chance of beginning within 24 hours of an infusion. Out of the 78 temporally related AEs, 73 (93.6%) were deemed unrelated to simoctocog alfa, 4 (5.1%) were deemed unlikely to be related and 1 (1.3%) [mild back pain] was deemed possibly related.

7.6.2.3. Treatment-related adverse events (adverse drug reactions)

Two (2) treatment-related AEs were reported in two patients. One (1) patient [information redacted] experienced one possible treatment-related AE of back pain (mild intensity) after 2 EDs to simoctocog alfa, and one (1) patient [information redacted]experienced one possible treatment-related AE of headache (mild intensity) after 4 EDs to simoctocog alfa. Both treatment-related AEs were reported to have resolved. As discussed in the review of AEs occurring in the total safety population, the IDMC identified 6 additional AEs in 5 patients in GENA-03 as being “possibly related” to simoctocog alfa (see Table 54, below). Therefore, 7 (11.9%) patients in the study experienced 8 (6.5%) events considered to be possibly related to simoctocog alfa as judged by investigators and/or the IDMC.

Table 54: GENA-03 - Additional AEs considered by IDMC assessment to be possibly or probably related to treatment.

Date	AE	SAE Yes/No	Intensity	Resolved Yes/No	Causality*
18-Jan-2012	Chills	No	Mild	Yes	Possible
22-Jun-2012	Rash	No	Mild	Yes	Possible
20-Jun-2011	Chills	No	Moderate	Yes	Possible
21-Apr-2012	Chills	No	Moderate	Yes	Possible
19-Aug-2011	Rash	No	Mild	Yes	Possible
19-Dec-2011	Rash	No	Mild	Yes	Possible

† All AEs were judged as unrelated by the Investigator, but possibly related by the IDMC. AE = adverse event; IDMC = independent drug monitoring committee; SAE = serious adverse event.

7.6.3. Deaths and other serious adverse events (SAEs)

7.6.3.1. Deaths

No deaths occurred during the study.

7.6.3.2. Other serious adverse events (SAEs)

There were 7 SAEs in 5 patients (see Table 55, below). Of the 7 SAEs, 2 were mild and 5 were moderate in severity. The 7 events were rated as serious because each required hospitalisation. All 5 patients remained in the study and completed between 87 and 109 EDs (that is, each of them received at least 75 infusions after the onset of their respective SAEs).

Table 55: GENA-03 - serious adverse events (SAEs).

Age, years	MedDRA PT	Reason for seriousness	Outcome	Causality
3	Device-related infection	Required hospitalisation	Recovered/ Resolved	Not related
3	Head injury	Required hospitalisation	Recovered/ Resolved	Not related
5	Head injury	Required hospitalisation	Recovered/ Resolved	Not related
4	Acute tonsillitis	Required	Recovered/	Not

Age, years	MedDRA PT	Reason for seriousness	Outcome	Causality
		hospitalisation	Resolved	related
	Upper RTI	Required hospitalisation	Recovered/ Resolved	Not related
	Lower RTI	Required hospitalisation	Recovered/ Resolved	Not related
10	Haemarthrosis	Required hospitalisation	Recovered/ Resolved	Not related

7.6.4. Discontinuations due to adverse events

There were no discontinuations due to AEs.

7.6.5. Laboratory tests

7.6.5.1. Immunogenicity

No FVIII inhibitors were detected in any patient at any time point during the study. Non-inhibitory antibodies against FVIII were detected in 2 patients, and in both patients the non-inhibitory antibodies were detected at screening. Efficacy of treatment with simoctocog alfa was rated as excellent in both patients with non-inhibitory FVIII antibodies. Further information on these two patients is provided in the review of immunogenicity in the total safety population reviewed previously in this CER.

7.6.5.2. Other laboratory tests (haematology and biochemistry)

Three (3) patients had a total of 30 haematological abnormalities classed as clinically significant; 1 patient with 1 abnormality (low Hct); 1 patient with 21 abnormalities (relating to low RBC, low Hct and low Hb); and 1 patient with 8 abnormalities (relating to low Hct and low Hb). All three patients had a history of iron deficiency anaemia/anaemia, and no AEs were reported relating to the haematological laboratory abnormalities for the 3 patients. Further information on these 3patients is provided in the review of other laboratory tests in the total safety population provided previously in this CER.

7.6.6. Vital signs

No clinically relevant abnormalities in vital signs (blood pressure, pulse rate, temperature) were observed.

7.7. Post-marketing experience

Not applicable. Simoctocog alfa was not marketed in any country at the time of the submission.

7.8. Evaluator's overall conclusions on safety

The safety of simoctocog alfa for the treatment of severe haemophilia A has been satisfactorily established in 135 patients, including 59 patients aged 2 to 12 years (29 aged 2-5 years, 30 aged 6-12 years). However, based on the "rule of three" it is unlikely that adverse reactions associated with simoctocog alfa and occurring with an incidence of < 2% have been detected in the total safety population of 135 patients.[8,9]

The pooled safety data from the 5 clinical studies have been reviewed. In addition, the safety data in children aged 2-12 years from GENA-03 have been separately reviewed. The mean age of

the 135 patients in the five clinical studies ranged from 6 to 40 years, and the overall age ranged from 2 to 75 years. Nearly all patients in the studies were "white". The safety profiles from the total safety population and from the paediatric safety population are consistent.

In the total safety population, 135 patients underwent treatment with simoctocog alfa. These patients received total mean doses of simoctocog alfa ranging from 104,813 to 585,489 IU (1835 to 6289 IU/kg) administered by total mean number of infusions ranging from 54.9 to 228 over total mean EDS ranging from 53.3 to 226, and over total mean treatment periods ranging from 179.9 to 455.6 days.

In the four studies with prophylaxis data, 113 patients received prophylactic treatment with simoctocog alfa with mean doses ranging from 32.8 to 38.9 IU/kg per infusion for a total of approximately 14,000 EDs. In the long-term study GENA-04, the average duration of treatment was 455.61 days (range: 33, 563 days), and the 18 patients in the study received simoctocog alfa over a total of 3,940 EDs. In the five studies with relevant data, the mean dose of simoctocog alfa for the on-demand treatment of BEs ranged from 32.3 to 45.1 IU/kg per infusion and from 35.1 to 50.2 IU/kg per infusion for surgical prophylaxis.

Of the 135 patients in the total safety population, 79 (58.5%) patients experienced a total of 272 AEs. In this population, AEs occurring in ≥ 2% of patients (that is, ≥ 3 patients) in descending order of frequency were nasopharyngitis (8.1%), pyrexia (7.4%), headache (7.4%), rhinitis (5.2%), cough (4.4%), diarrhoea (3.7%), chills (3.7%), injury (3.7%), rash (3.7%), abdominal pain (3.0%), varicella (3.0%), arthralgia, (3.0%), back pain (3.0%), bronchitis (2.2%), upper RTI (2.2%), and head injury (2.2%).

The investigators identified 5 (3.7%) patients with 8 AEs classified as treatment-related. These included injection site pain in 1 patient, back pain in 1 patient, headache in 1 patient, anti-FVIII antibody in 1 patient, and vertigo, dry mouth, paraesthesia, and injection site pain all in the same patient. In addition, review of the paediatric data from GENA-03 by the IDMC identified a further 6 AEs in 5 patients which were judged to be "possibly" related to treatment (3 patients each with the AE of chills, 2 patients with the AE of rash on 2 separate occasions, 1 patient with the AE of rash). There were no inconsistencies between investigator and IDMC safety assessments in studies GENA-01, GENA-08, GENA-09 or GENA-04. In the total safety population, 10 (7.4%) patients experienced 14 (5.1%) AEs judged to be possibly or probably related to simoctocog alfa by investigators and/or the IDMC. All of the treatment-related AEs recovered/resolved without sequelae, apart from 1 event of anti-FVIII antibody positive for which the outcome was unknown.

One death occurred in the total safety population and was considered to be unrelated to treatment (acute respiratory and cardiovascular failure associated with status epilepticus in 1 patient with a known history of epilepsy). Excluding the one death, there were 11 other SAEs in 8 patients and all events were considered to be unrelated to treatment. The 11 SAEs included depression/suicidal in 1 patient, traumatic fracture in 1 patient, device-related infection in 1 patient, head injury in 2 patients, haemarthrosis in 1 patient, hepatic encephalopathy/hepatic cirrhosis in 1 patient, and acute tonsillitis/upper RTI/lower RTI in 1 patient. All 11 SAEs recovered/resolved, except for the one event of hepatic cirrhosis. Withdrawals from treatment (all reasons) were reported in 7 (5.1%) patients, and withdrawal due to AEs occurred only in the one patient who died during the study.

The immunogenicity of simoctocog alfa was assessed throughout each of the studies, and no FVIII inhibitors were identified in any of the 135 patients in the safety population. Non-inhibitory anti-rhFVIII antibodies were identified in 4 patients, including 3 patients who were positive at screening. The efficacy of simoctocog alfa was judged as excellent in all 4 patients with non-inhibitory FVIII antibodies. In the SOC of "immune system disorders" there was 1 case of allergic oedema in a paediatric patient, and 1 case of seasonal allergy in an adult patient. No

AEs relating to hypersensitivity disorders were reported. No thromboembolic events were reported.

Clinically significant laboratory abnormalities (haematological, biochemical, urinalysis) were uncommon, as were clinically significant abnormalities in vital signs. No patients were found to be positive for HBV or HCV infection during the study.

There were no safety studies with simoctocog alfa in patients with hepatic or renal impairment. There were no drug-drug interaction studies involving simoctocog alfa. There were no safety data in patients younger than 2 years of age or older than 75 years of age. There were no safety data in racial groups other than that classified as "while". There were no safety data in female patients. There were no safety data in previously untreated patients with severe haemophilia A.

8. First round benefit-risk assessment

8.1. First round assessment of benefits

The benefits of simoctocog alfa for routine prophylaxis, treatment of breakthrough BEs, and prophylactic use in surgical procedures have been satisfactorily established in previously pre-treated adults and children (aged 2-12 years) with severe haemophilia A (FVIII:C < 1%). However, there were no data in the submission in children aged < 2 years of age, and there were only 2 patients in the submitted data who were aged 65 years or older. Nearly all patients in the studies were "white", and there were no data on the benefits of treatment in other racial groups. There were no data in female patients, however, as the disease occurs almost exclusively in males this deficiency is not considered to be significant. In terms of FVIII genotypes, most known FVIII gene mutations were single occurrence with the exception of intron 22 inversions. There were no data on previously untreated patients with severe haemophilia A.

The benefits of treatment outlined below are based of the data from the three pivotal studies (2 adult, 1 paediatric). The adult patients from the two supportive single-centre Russian studies differed from the adult patients from the two pivotal studies due to the presence of severe pre-existing joint disease, which the sponsor considers to be due to inadequate treatment. Nevertheless, the benefits of treatment with simoctocog alfa for patients in the Russian study are considered to be satisfactory.

8.1.1. Prophylaxis

In the pivotal study in previously treated adults investigating simoctocog alfa as prophylaxis (GENA-08), the percentage of patients experiencing BEs while on prophylaxis was 50% (16/32), the number of exposure days (mean±SD) was 85.1±15.4, and the overall mean monthly BE rate was 0.188 (range: 0, 1.21) (spontaneous BEs/month 0.095 [range: 0, 0.71]; traumatic BEs/month 0.082 [range: 0, 0.68]). In this study, the overall efficacy of prophylactic treatment with simoctocog alfa as regards **all** BEs was classed as excellent (< 0.75 BEs/month) in 90.6% (n=29) of patients, good (BEs 0.75 - 1.0 BEs/month) in 6.3% (n=2) of patients, and moderate (> 1.0 - 1.5 BEs/month) in 3.1% (n=1) of patients. Using the same efficacy criteria for spontaneous BEs, the efficacy of prophylactic treatment was classed as excellent in all 32 patients (100%).

In the pivotal study in previously treated children aged 2-12 years investigating simoctocog alfa as prophylaxis (GENA-03), the percentage of patients experiencing BEs while on prophylaxis was 54.2% (32/59), the number of exposure days (mean±SD) was 89.8±22.3, and the overall monthly BE rate was 0.338 (range: 0, 1.70) (spontaneous BEs/month 0.123 [range: 0, 1.13]; traumatic BEs/month 0.192 [range: 0. 1.53]). The risk of experiencing a traumatic BE was greater than the risk of experiencing a spontaneous BE, which is not unexpected in children aged 2 to 12 years. The efficacy of prophylactic treatment with simoctocog alfa for **all** BEs was classed as excellent (< 0.75 BEs/month) in 83.1% (49/59) of patients, good (0.75 - 1.0

BEs/month) in 8.5% (3/59) of patients, moderate (> 1.0 - 1.5 BEs/month) in 5.1% (3/59) of patients, and poor (≥ 1.5 BEs/month) in 3.4% (2/59) of patients. Using the same efficacy criteria for spontaneous bleeds, 94.9% (56/59) of patients had excellent efficacy, 1.7% (1/59) had good efficacy, and 3.4% (2/59) had moderate efficacy. The efficacy of prophylactic treatment with simoctocog alfa was better in the subgroup of children aged 2-5 years compared with the sub-group of children with aged 6 -12 years with respect to any BEs, spontaneous BEs and traumatic BEs.

8.1.2. On-demand treatment for BEs in patients not receiving prophylaxis

In the pivotal study of on-demand treatment in previously treated adults not receiving routine prophylaxis (GENA-01), the 22 patients enrolled in the study experienced a total of 986 BEs treated with simoctocog alfa. Of the 986 BEs, 65.1% (n=642) were spontaneous, 34.6% (n=341) were traumatic, and 0.3% (n=3) were due to other causes. In total, 42.2% (n=416) of the BEs were classed as minor, 57.4% (n=566) were classed as moderate to major and 0.3% (n=3) were classed as major to life-threatening. Overall, the mean duration of treatment of BEs overall was 1.1±0.75 days (range: 1, 19 days). The median number of infusions administered to treat a BE was 1.0 (range: 1, 13) and the mean±SD dose per infusion was 32.3±10.6 IU/kg. The proportion of BEs requiring 1 infusion was 91.4% (841/986) and the proportion of BEs requiring 2 infusions was 5.8% (53/986). For all 986 BEs, personal efficacy was classed as excellent for 60.3%, good for 34.1% and moderate for 5.5%. For the 416 minor BEs, personal efficacy was classed as excellent for 75.0%, good for 23.6%, and moderate for 1.4%. For the 566 moderate to major BEs, personal efficacy was classed as excellent for 50.0%, good for 41.7%, and moderate for 8.3%. For the 3 major to life-threatening BEs, personal efficacy was classed as excellent for 66.7% and moderate for 33.3%.

8.1.3. On-demand treatment for breakthrough BEs in patients receiving prophylaxis

In the pivotal study in previously treated adults assessing breakthrough BEs while on prophylactic treatment with simoctocog alfa (GENA-08), 15 of the 32 patients experienced 30 BEs requiring treatment with simoctocog alfa. The median number of simoctocog alfa infusions administered to treat a BE was 1.0 (range: 1, 12) and the mean±SD dose per infusion was 33.3±6.7 IU/kg. The proportion of the 30 BEs requiring only 1 or 2 infusions was 88.9% (1 infusion for 81.5% of BEs, 2 infusions for 7.4% of BEs). Personal efficacy assessments were available for 28 BEs, with 14 (50%) being classed a minor and 14 (50%) being classed as moderate to major. No BEs in this study were classed as major to life-threatening. For all 28 BEs, personal efficacy was rated as excellent for 71.4% (n=20) and good for 28.8% (n=8). For the 14 minor BEs, personal efficacy was rated as excellent for 85.7% (n=12) and good for 14.3% (n=2). For the 14 moderate to major BEs, personal efficacy was rated as excellent for 57.1% (n=8) and good for 42.9% (n=6). Overall, personal efficacy was rated as excellent or good for all 28 breakthrough BEs requiring treatment with simoctocog alfa.

In the primary study in previously treated children aged 2 to 12 years assessing breakthrough BEs while on prophylactic treatment with simoctocog alfa (GENA-03), 32 of the 59 patients experienced 108 BEs requiring treatment with simoctocog alfa. The median number of infusions administered to treat a BE was 1.0 (range: 1, 22) and the mean±SD dose per infusion was 45.1±12.6 IU/kg. The proportion of the 108 BEs requiring only 1 or 2 infusions was 81.3% (1 infusion for 68.6% of BEs, 2 infusions for 12.7% of BEs). Of the 108 BEs, 60.2% (n=65) were traumatic, 33.3% (n=65) were spontaneous, and 6.5% (n=7) were classified as "other". Of the 108 BEs, 56.5% (n=61) were classed as minor, 42.6% (n=46) as moderate to major and 1 (0.9%) was of unknown severity. There were no major to life threatening BEs. Of all 108 BEs, personal efficacy was rated as excellent for 71.3% good for 11.1%, moderate for 15.7%, and none for 1.9%. For the 61 minor BEs, personal efficacy was rated as excellent for 86.9%, good for 11.5%, and moderate for the remaining 1.6%. Overall, efficacy for all minor BEs was rated as at least moderate. For the 46 moderate to major BEs, personal efficacy was rated as excellent for 50.0%, good for 10.9%, moderate for 34.8%, and none for 4.3%.

In the paediatric study (GENA-03), sub-group analysis showed that the benefits of treatment with simoctocog alfa were applicable to children aged 2 to 5 years and aged 6 to 12 years. BEs occurring while on prophylactic treatment with simoctocog alfa occurred more frequently in children in the older age sub-group group compared with the younger age sub-group group. The efficacy of prophylactic treatment for all BEs was rated as excellent or good in 96.6% (93.1% and 3.4%, respectively) children in the younger age sub-group and 86.7% (73.3% and 13.3%, respectively) of children in the older age sub-group. Furthermore, the efficacy of prophylactic simoctocog alfa treatment for spontaneous BEs was rated as excellent in the majority of patients in both the younger and older age sub-groups (96.6% vs 93.3%, respectively).

In the sub-group analysis based on age (GENA-03), of the 108 breakthrough BEs treated with simoctocog alfa, 33 (30.6%) occurred in the 2-5 years sub-group and 75 (69.4%) occurred in the 6-12 years sub-group. For all breakthrough BEs treated with simoctocog alfa efficacy in the 2-5 years (n=33) sub-group vs the 6-12 years (n=75) sub-group, efficacy was rated as excellent for 63.6% vs 74.7%, good for 18.2% vs 8.0%, moderate for 18.2% vs 14.7%, and none for 0% vs 2.7%. For the minor breakthrough BEs treated with simoctocog alfa in the 2-5 years (n=20) sub-group vs the 6-12 years (n=41) sub-group, efficacy was rated as excellent for 75.0% vs 92.7%, good for 25.0% vs 4.9%, moderate for 0% vs 2.4%, and none for no patients in either sub-group. For moderate to major breakthrough BEs treated with simoctocog alfa in the 2-5 years (n=13) sub-group vs the 6-12 years (n=33) sub-group, efficacy was rated as excellent for 46.2% vs 51.5%, good for 7.7% vs 12.1%%, moderate for 46.2% vs 30.3%, and none for 0% vs 6.1%.

8.1.4. Surgical prophylaxis

In the total patient population from the five submitted studies (adults and children), 19 patients underwent 33 surgical procedures. For all surgical procedures combined (that is, minor and major), efficacy was rated as excellent for 87.9% (29/33), good for 9.1% (3/33), and moderate for 3.0% (1/33). All 33 surgical procedures were reported as having at least moderate efficacy. For the 13 major surgical procedures in 12 patients, efficacy was rated as excellent for 69.2% (9/13), good for 23.1% (3/13), and moderate for 7.6% (1/13). In the paediatric study (GENA-03), 6 patients (5 with haemophilia A and 1 with VWD) underwent 6 planned major surgical procedures. In all 5 surgical procedures in the 5 children with haemophilia A overall efficacy was rated as excellent by both the surgeon and the haematologist.

8.2. First round assessment of risks

The risks of simoctocog alfa have been investigated in 135 previously treated male patients with severe haemophilia A aged 2 to 75 years, including 59 patients aged 2 to 12 years of age. It is considered that the risks of treatment with simoctocog alfa are acceptable for the proposed indications in patients aged 2 years and above. There are no safety data in patients aged < 2 years or aged > 75 years. There are no safety data in previously untreated patients with severe haemophilia A.

None of the 135 patients in the total safety population had developed FVIII inhibitors (that is, neutralising antibodies) at the data-lock point, but it is possible that longer periods of exposure to simoctocog alfa might result in the formation of inhibitors in some patients. It has been estimated that the incidence of inhibitor development in previously treated patients with haemophilia A, treated on at least 150 EDs is ~2 per 1000 patient-years.[10]

The sponsor stated that no hypersensitivity or allergic reactions (including anaphylactic shock) were observed in any of the clinical studies. However, 5 cases of rash were reported in the total safety population, including 4 in the paediatric study (GENA-03). In addition, in GENA-03 the IDMC identified 3 cases of rash in 3 children and 3 cases of chills in 2 children as being "possibly" related to treatment with simoctocog alfa. Furthermore, there was 1 case of "allergic oedema" identified in the paediatric study GENA-03, and 2 cases of pruritus identified in GENA-01 (1 case, adult) and in GENA-03 (1 case, paediatric). Although no hypersensitivity or allergic

reactions have been reported in the safety population, the sponsor will be requested to provide further information on the cases of rash, chills, pruritus, and allergic oedema in order to clarify the nature of these events.

Of the 135 patients in the total safety population, 79 (58.5%) experienced a total of 272 AEs. None of the reported AEs are considered to raise safety signals for simoctocog alfa. In the total safety population, AEs occurring in ≥ 2% of patients (that is, ≥ 3 patients) in descending order of frequency were nasopharyngitis (8.1%), pyrexia (7.4%), headache (7.4%), rhinitis (5.2%), cough (4.4%), diarrhoea (3.7%), chills (3.7%), injury (3.7%), rash (3.7%), abdominal pain (3.0%), varicella (3.0%), arthralgia, (3.0%), back pain (3.0%), bronchitis (2.2%), upper RTI (2.2%), and head injury (2.2%). Increased ALT and AST levels were reported in 1 patient each, and no cases of increased serum creatinine were reported. No thromboembolic AEs were reported.

In the total safety population, there were 10 (7.4%) patients with 14 AEs (5.1%) judged by the investigator and/or IDMC to be possibly or probably related to simoctocog alfa (that is, 6 AEs in 3 adults; 8 AEs in 7 children). These 14 events included injection site pain in 1 patient, back pain in 1 patient, headache in 1 patient, anti-FVIII antibody in 1 patient, rash in 3 patients, chills in 2 patients, and vertigo, dry mouth, paraesthesia, and injection site pain all in the same patient. In the paediatric population (GENA-03), there were 7 (11.9%) patients with 8 (6.5%) AEs judged by the investigator and/or IDMC to be possibly or probably related to simoctocog alfa. These 8 events were 1 event of chills in each of 3 patients, 2 separate events of rash in 1 patient, 1 event of rash in 1 patient, 1 event of back pain in 1 patient, and 1 event of headache in1 patient.

One death occurred in the total safety population (acute respiratory and cardiovascular failure associated with status epilepticus in 1 patient with a known history of epilepsy), and this death was considered to be unrelated to treatment. Excluding death, there were 11 other SAEs in 8 patients and all events were considered to be unrelated to treatment. The 11 SAEs included depression/suicidal in 1 patient, traumatic fracture in 1 patient, device-related infection in 1 patient, head injury in 2 patients, haemarthrosis in 1 patient, hepatic encephalopathy/hepatic cirrhosis in 1 patient, and acute tonsillitis, upper RTI, and lower RTI all occurring in 1 patient. All 11 SAEs recovered/resolved except for the one case of hepatic cirrhosis, which had still not recovered/not resolved at the data cut-off date. Premature withdrawals from treatment (all reasons) were reported in 7 (5.1%) patients, and the only AEs resulting in withdrawal were those associated with the one death.

Clinically significant laboratory abnormalities (haematological, biochemical, urinalysis) were uncommon, as were clinically significant abnormalities in vital signs. No patients were found to be positive for HBV or HCV infection.

8.3. First round assessment of benefit-risk balance

The benefit-risk benefit for simoctocog alfa for the proposed indications is considered to be favourable for patients with severe haemophilia A in adults and children aged 2 years and older.

9. First round recommendation regarding authorisation

It is recommended that Nuwiq be approved for:

> *Treatment and prophylaxis of bleeding (also during and after surgery) in previously treated patients with haemophilia A (congenital factor VIII deficiency).*
>
> *Nuwiq is also indicated in haemophilia A patients with known allergic reactions to mouse or hamster protein, in which hamster cell derived rFVIII are contraindicated.*

Nuwiq is appropriate for use in adults and children aged 2 years and above. There are no data in children (including newborns) under the age of 2 years.

Comment: The indication should refer to previously treated patients, as there are no data in untreated patients with severe haemophilia A. It is not recommended that NUWIQ be approved for use in children under the age of 2 years (including newborns) as there are no PK, efficacy, or safety data for the product in this patient population. The sponsor indicates that children under the age of 2 years are eligible to participate in on-going study GENA-05 which is enrolling previously untreated patients with severe haemophilia A with no age restrictions. The submission indicates that a post-authorisation study to document the long-term immunogenicity, safety and efficacy of simoctocog alfa in patients with haemophilia A treated in routine clinical practice is planned to start in Q2, 2015 (GENA-99).

10. Clinical questions

10.1. Pharmacokinetics

1. For GENA-03, please provide the demographic characteristics of the 26 patients included in the PK-PP population.

10.2. Pharmacodynamics

No questions submitted.

10.3. Efficacy

2. In GENA-03, for prophylaxis children were treated with simoctocog alfa every other day or 3 times a week. Does the sponsor have any data comparing the efficacy of the every other day versus 3 times a week regimens? Please comment on the potential efficacy difference between the two regimens in children aged 2 to 12 years.
3. In GENA-03, please provide the number and percentage of children with plasma FVIII:C ≥ 0.01 IU/mL before the first PK and IVR assessments as assessed by both the CHR and OS assays, and compare these results with the corresponding assessments obtained in the screening period.
4. It was stated that GENA-04 was terminated prematurely due to substantial changes in data requirements introduced by the Russian authorities. What were the changes in the data requirements required by the Russian authorities?

10.4. Safety

5. How long after the last dose of simoctocog alfa were adverse event data collected in the five submitted studies with safety data (for example, were events occurring up to and including 30 days after the last dose considered to be treatment-emergent adverse events)?
6. In the total safety population (n=135), 5 cases of rash were identified (1 in GENA-01, 4 in GENA-03). The IDMC identified 3 cases of rash (2 separate events in 1 patient, 1 event in 1 patient) in GENA-03 as being "possibly" related to treatment. Does the sponsor have any information on the 5 cases of rash identified in the safety population? In particular, can it be determined if any of the rashes were likely to be hypersensitivity or allergic reactions to simoctocog alfa (for example, urticaria)?

7. In GENA-03, 3 cases of chills (1 event in each of 3 paediatric patients) were reported by the IDMC as "possibly" related to treatment with simoctocog alfa. Please explain why these events are not considered to be hypersensitivity reactions?
8. In the total safety population (n=135), 2 cases of pruritus were identified (1 in GENA-01, 1 in GENA-03). Does the sponsor have any information on the 2 cases of pruritis identified in the safety population? In particular, can it be determined if these cases were likely to be hypersensitivity or allergic reactions to simoctocog alfa.
9. In GENA-03 (n=59), 1 paediatric patient was identified has having "allergic oedema". Does the sponsor have any information on this case? In particular, what part of the body was involved and was the reaction an allergy to simoctocog alfa?
10. Please comment on potential hypersensitivity and allergic reactions to simoctocog alfa identified in the total safety population (all five studies) and in the paediatric population (GENA-03). Have any analyses of the safety data been undertaken using MedDRA search criteria for "hypersensitivity" (SMQ), "anaphylactic reactions" (SMQ), or "allergic conditions" (HLGT)?

11. Second round evaluation of clinical data submitted in response to questions

11.1. Clinical questions

11.1.1. Pharmacokinetics

11.1.1.1. Question 1

For GENA-03, please provide the demographic characteristics of the 26 patients included in the PK-PP population.

11.1.1.1.1. Sponsor's response (complete)

The demographic characteristics of the 26 patients included in the PK-PP population are shown in Table 56.

Table 56: Population demographics

Parameter	N (%)	Mean ± SD	Median (Range)
Age group: 2–<6	13 (50.0)		
6-12	13 (50.0)		
Total	26 (100.0)		
Age at first study treatment	26 (100.0)	6.1 ± 3.2	5.5 (2-12)
Height (cm)	26 (100.0)	120.9 ± 22.5	114.5 (92-172)
Weight (kg)	26 (100.0)	25.5 ± 13.8	21.0 (13-73)
Body Mass Index (kg/m²)	26 (100.0)	16.3 ± 2.6	15.8 (13-27)
Race: White	26 (100)		
Blood type: 0	11 (42.3)		
A	9 (34.6)		
AB	1 (3.8)		
B	5 (19.2)		
Gene defect:	26 (100.0)		
Exon 14 c. 3934dup. T Cys1293fsX7:	1 (3.8)		
Intron-22 Inversion	13 (50.0)		
Missense mutation	4 (15.4)		
No mutation found	2 (7.7)		
Nonsense mutation	2 (7.7)		
Small deletion/insertion	4 (15.4)		
Family haemophilia history			
No	15 (57.7)		
Yes	11 (42.3)		
Family inhibitor history			
No	24 (92.3)		
Yes	2 (7.7)		

N = number of patients; PK = pharmacokinetics; PP = per protocol; SD = standard deviation. Source: GENA-03 study report

11.1.1.1.1.1. Clinical evaluator's comment

The sponsor's response is satisfactory. The patients in the study were equally divided between those aged 2 to < 6 years and those aged 6 to 12 years. The median age at first study treatment was 5.5 years. There were no patients aged < 2 years or > 12 years.

11.1.2. Efficacy

11.1.2.1. Question 1

In GENA-03, for prophylaxis children were treated with simoctocog alfa every other day or 3 times a week. Does the sponsor have any data comparing the efficacy of the every other day versus 3 times a week regimens? Please comment on the potential efficacy difference between the two regimens in children aged 2 to 12 years.

11.1.2.1.1. Sponsor's response (complete)

Originally, the protocol stipulated that patients be treated prophylactically every other day. The three times per week treatment was included as an option in protocol amendment no. 1 at a time when already approximately 60% of patients were enrolled into the study.

As assignment to "Every other day treatment" or "Three times per week" subgroups was not formally captured in the Case Report Form, and patients were allowed to switch from one treatment regimen to the other, we assigned patients retrospectively to these subgroups using as criterion the frequency of certain simoctocog alfa prophylactic infusion intervals. Listing Australia_EFF1.1 displays the frequencies of simoctocog alfa prophylactic infusion intervals ≤ 2 days versus ≥ 3 days by subject and Listing Australia_EFF1.2 displays the frequency of ≤ 2 day infusion interval in descending order.

- All patients with a proportion of more than 80% of prophylactic infusions given ≤ 2 days were assigned to subgroup "Every other day" (n =38, 64.4%).
- All patients with a proportion of less than 80% but more than 50% of prophylactic infusions given ≤ 2 days were assigned to subgroup "Three times a week" (n = 17, 28.8%).
- For four patients (6.8%), no clear assignment to either of these subgroups was possible, see also footnote on Listing Australia_EFF1.1.

Tables Australia_EFF1.1.1.1 through to Australia_EFF1.3.4.3 show the overall efficacy assessments of prophylactic treatment for each subgroup after 50 Exposure Days and at the end of study by type (spontaneous, traumatic), site and severity of bleeding and also by time distance from last study drug administration, both for the PROP and the PROP-PP population.

The monthly rate of bleeding episodes at the end of the study of the PROP population is summarised in Table 57.

Table 57: Monthly bleeding rate at the end of study (PROP population)

Bleed type	Every other day (n = 38)	Three times a week (n = 17)	No clear assignment (n = 4)
All bleeds Mean ± SD Median (range)	0.40 ± 0.49 0.16 (0, 1.70)	0.21 ± 0.29 0 (0, 0.81)	1.5 ± 1.3 1.5 (0, 3)
Spontaneous bleeds	0.18 ± 0.32	0.04 ± 0.12	0 ± 0

Bleed type	Every other day (n = 38)	Three times a week (n = 17)	No clear assignment (n = 4)
Mean ± SD Median (range)	0 (0, 1.13)	0 (0, 0.48)	0 (0, 0)
Traumatic bleeds Mean ± SD Median (range)	0.21 ± 0.32 0.14 (0, 1.53)	0.15 ± 0.24 0 (0, 0.8)	0.16 ± 0.23 0.08 (0, 0.49)

PROPH = study population of patients receiving prophylaxis with simoctocog alfa; SD = standard deviation.

The data for the PROP-PP are similar to those of the PROP population.

The monthly bleeding episode rate for the patients in the “Three times a week” subgroup appears less than in those belonging to the “Every other day” subgroup. While this looks at first glance unexpected, the reason for this is most likely related to; the arbitrary definition we used to retrospectively select patients with a seemingly 3 times/week interval, the relatively low number of patients in the 3 times/week group, and the non-randomised design of this assignment so that by chance more patients with a higher bleeding frequency (due to for example individual shorter product half-life) are in the 2 times/week group. All supportive documents as highlighted above in grey are included in Module 1.0.2 “Supportive clinical listings and tables”.

11.1.2.1.1.1. Clinical evaluator's comment

The sponsor's response indicates that the monthly bleeding rate at the end of the study was lower in the prophylactic paediatric population (PROP) receiving simoctocog alfa "three times a week" (n=17) compared with the population receiving simoctocog alfa "every other day" (n=38). This relationship between the two treatment groups was observed for all types of bleeds and for spontaneous and traumatic bleeds. Similar results were also seen in the per-protocol prophylactic paediatric population (PROP-PP) receiving simoctocog alfa "three times a week" (n=17) or "every other day" (n=34).

The overall efficacy assessment of prophylactic treatment at the end of the study for the PROP is summarised below in Table 58 and shows that treatment "three times a week" was marginally superior to treatment every other day". Similar results were also seen in the PROP-PP. The sponsor has discussed the potential reasons for the unexpected result of greater efficacy in the "three times a week" prophylactic treatment group compared with the "every other day" group prophylactic treatment group. It is noted that the study did not include randomized allocation to the two treatment groups. Consequently, the comparison between the two treatment groups is might be subject to bias both identified and unidentified. However, the provided comparative data suggest that both the "every other day" and the "three times a week" prophylactic regimens in paediatric patients are clinically efficacious.

Table 58: Monthly response rate with prophylactic treatment at the end of the study in the prophylactic paediatric population.

Type of BE	Monthly response rate	All (n=38)	All (n=17)	All (n=4)
		Every other day	Three times a week	No clear assignment
Spontaneous	Excellent (monthly rate < 0.75)	35 (92.1%)	17 (100%)	4 (100%)
	Good (monthly rate 0.75 to ≤ 1	1 (2.6%)	-	-
	Moderate (monthly rate > 1 to 1.5)	2 (5.3%)	-	-
	Poor (monthly rate > 1.5)	-	-	-
Traumatic	Excellent (monthly rate < 0.75)	35 (92.1%)	16 (94.1%)	4 (100%)
	Good (monthly rate 0.75 to ≤ 1	2 (5.3%)	1 (5.9%)	-
	Moderate (monthly rate > 1 to 1.5)	1 (2.6%)	-	-
	Poor (monthly rate > 1.5)	-	-	-
All	Excellent (monthly rate < 0.75)	30 (78.9%)	15 (88.2%)	4 (100%)
	Good (monthly rate 0.75 to ≤ 1	3 (7.9%)	2 (11.8%)	-
	Moderate (monthly rate > 1 to 1.5)	3 (7.9%)	-	-
	Poor (monthly rate > 1.5)	2 (5.3%)	-	-

11.1.2.2. Question 2

In GENA-03, please provide the number and percentage of children with plasma FVIII:C ≥ 0.01 IU/mL before the first PK and IVR assessments as assessed by both the CHR and OS assays, and compare these results with the corresponding assessments obtained in the screening period.

11.1.2.2.1. Sponsor's response (complete)

The requested analysis is provided in Table 59.

Table 59: Number and percentage of children with plasma FVIII:C≥0.01 IU/mL at screening and at baseline (before the first PK and IVR assessments), ITT population (n=59)

Assay	Screening N (%) of patients with FVIII:C ≥ 0.01 IU/mL	Baseline N (%) of patients with FVIII:C ≥ 0.01 IU/mL
Chromogenic	19 (32.2)	25 (42.4)
One-stage	41 (69.5)	42 (28.8)

Baseline values are defined as the pre-injection FVIII:C value for the 1st PK/1st recovery assessment. In cases where this assessment was on the same day as the screening visit usually only one FVIII:C measurement was done before study drug administration. In these cases the respective values appear both under Screening and under Baseline.

All patients included in this study had been diagnosed with severe haemophilia A except one patient who was later found to suffer from von Willebrand disease.

11.1.2.2.1.1. Clinical evaluator's comment

The sponsor's response is satisfactory. The inconsistency between the "chromogenic" and "one-stage" assays is noted. The sponsor comments that all patients had been diagnosed with severe haemophilia A (that is, inclusion criteria required FVIII:C < 1%), except one with von Willebrand disease. Presumably the observed FVIII: C ≥ 1% levels at screening and baseline were due to carry-over effects from prior FVIII treatment.

11.1.2.3. Question 3

It was stated that GENA-04 was terminated prematurely due to substantial changes in data requirements introduced by the Russian authorities. What were the changes in the data requirements required by the Russian authorities?

11.1.2.3.1. Sponsor's response (complete)

Study GENA-09 started in March 2009. Originally, it was planned to use the clinical data from this mono-centre (Moscow) study for submission of the marketing authorisation application in Russia and to continue treating the GENA-09 patients in the extension study GENA-04 until marketing authorisation of simoctocog alfa in Russia was granted. However, at the end of 2010 a new law was implemented in Russia (The Federal Law N61 dated 12.04.2010, published on 14.04.2010 and which came into effect from 1st of September 2010) requesting that a multi-national study involving at least one centre in Russia is required to obtain marketing authorisation, which would have resulted in a delay of several years. Under these circumstances, it became economically unfeasible to continue study GENA-04 and it was stopped in July 2011. Submission for marketing authorisation of simoctocog alfa in Russia is now expected in the 2nd half of 2014.

11.1.2.3.1.1. Clinical evaluator's comment

The sponsor's response is satisfactory.

11.1.3. Safety

11.1.3.1. Question 1

How long after the last dose of simoctocog alfa were adverse event data collected in the five submitted studies with safety data (for example, were events occurring up to and including 30 days after the last dose considered to be treatment-emergent adverse events)?

11.1.3.1.1. Sponsor's response (complete)

In all five studies adverse events were collected until the final visit, which usually coincided with the last administration of simoctocog alfa in the study. All five study protocols mentioned the following under “Other relevant safety information” and “Post-study related safety reports”:

“Any ADR (i.e. any AE with a suspected causal relationship to the IMP) which occurs after

the completion of the study should be reported by the investigator. The usual procedure for reporting post marketing safety information should be followed, but relation to the clinical study should be stated on the report.

If a subject dies within 4 weeks after the last study drug administration, this should be reported as well, without respect of being considered treatment-related or not."

Following the final visit more than half of the 135 patients who participated in these five studies continued treatment with simoctocog alfa in extension studies to assess the long-term immunogenicity, safety and efficacy of simoctocog alfa: Three of the 22 GENA-01 patients, 18 of the 22 GENA-09 patients and 49 of the 59 paediatric patients switched to the respective extension studies GENA-11, GENA-04 and GENA-13.

11.1.3.1.1.1. Clinical evaluator's comment

The sponsor's response is satisfactory.

11.1.3.2. Question 2

In the total safety population (n=135), 5 cases of rash were identified (1 in GENA-01, 4 in GENA-03). The IDMC identified 3 cases of rash (2 separate events in 1 patient, 1 event in 1 patient) in GENA-03 as being "possibly" related to treatment. Does the sponsor have any information on the 5 cases of rash identified in the safety population? In particular, can it be determined if any of the rashes were likely to be hypersensitivity or allergic reactions to simoctocog alfa (for example, urticaria)?

11.1.3.2.1. Sponsor's response (abridged)

Information on the 6 cases of rash in 5 patients ([information redacted] experienced rashes twice) in the safety population is provided [in the response document]. The IDMC had judged the mild rashes for patients [information redacted] as "possibly" related to treatment because of the temporal relationship between the event and IMP administration (GENA-03 Clinical Study Report). The Investigators who reported the mild rashes for patients [information redacted] were contacted with regards to the potential allergic symptoms following the administration of the IMP. They confirmed their previous assessment of relationship: the rashes were not related to the IMP. In addition, a narrative was prepared for the adverse events related to patient [information redacted] based on the available information.

11.1.3.2.1.1. Clinical evaluator's comment

The five clinical narratives for patients with rash provided by the sponsor in the response document have been examined. The sponsor concluded that "all rashes were mild and considered 'not related' by the investigator. Therefore, [the sponsor considered] it was very unlikely that any of these rashes were hypersensitivity or allergic reactions to simoctocog alfa." The sponsor's response is considered to be acceptable.

11.1.3.3. Question 3

In GENA-03, 3 cases of chills (1 event in each of 3 paediatric patients) were reported by the IDMC as "possibly" related to treatment with simoctocog alfa. Please explain why these events are not considered to be hypersensitivity reactions?

11.1.3.3.1. Sponsor's response (abridged)

The IDMC had judged these adverse events as "possibly" related because of the temporal relationship between the event and IMP administration.

The Investigators who reported the chills were contacted with regards to the above potential allergic symptoms following the administration of the IMP. They reviewed the narratives and confirmed their previous assessment of the relationship: the chills are all not related to the IMP.

11.1.3.3.1.1. Clinical evaluator's comment

The two clinical narratives for patients with chills provided by the sponsor in the response document have been examined. No clinical narrative was provided for one of the two Russian patients considered by the sponsor to have had a wrong translation/interpretation of "acute upper respiratory tract infection" recorded as "chills" in the CRF. The sponsor considered that from its "point of view there is no increased risk of potential allergic symptoms in the paediatric population". Based on the data provided by the sponsor it appeared to be unlikely that the reported adverse events of "chills" are hypersensitivity reactions to simoctocog alfa.

11.1.3.4. Question 4

In the total safety population (n=135), 2 cases of pruritus were identified (1 in GENA-01, 1 in GENA-03). Does the sponsor have any information on the 2 cases of pruritis identified in the safety population? In particular, can it be determined if these cases were likely to be hypersensitivity or allergic reactions to simoctocog alfa.

11.1.3.4.1. Sponsor's response (complete)

[information redacted] had a mild unrelated pruritus starting on 15 December 2010 with an unknown end date. This patient underwent surgery (revision of total right knee) on 14 December 2010. According to the nurse the itching was related to the narcotics the patient received. The itching started after the intravenous administration of dilaudid which is well known to cause pruritus.

[information redacted] had a mild unrelated pruritis ("itchy foot"), which started on 6 January 2012 and ended on 8 January 2012 after 12 Exposure Days. The study site was contacted again in April 2014 and confirmed that this event was not IMP related as it occurred too long after study start and also too long after the last infusion. In addition, it did not reoccur with continued treatment with simoctocog alfa, neither during the remainder of GENA-03 (until 6 June 2012) nor during the ongoing extension study GENA-13 so far.

From the Applicants point of view there is no increased risk of potential allergic symptoms in the paediatric population.

11.1.3.4.1.1. Clinical evaluator's comment

The sponsor's response is satisfactory.

11.1.3.5. Question 5

In GENA-03 (n=59), 1 paediatric patient was identified has having "allergic oedema". Does the sponsor have any information on this case? In particular, what part of the body was involved and was the reaction an allergy to simoctocog alfa?

11.1.3.5.1. Sponsor's response (complete)

[information redacted] was included into study GENA-03 in January 2012 when he was 4 years old. He was previously treated with a full-length rFVIII. On 25-Jun-2012, after 62 Exposure Days, an allergic oedema of the left hand was reported, which resolved on 26-Jun-2012 after 0.5 days. This adverse event was judged as moderate and not related to treatment with simoctocog alfa. The last administration of simoctocog alfa was given 58.33 hours before this adverse event occurred (GENA-03 Clinical Study Report, Listing 16.2.7.1). The allergic oedema was treated with a single dose of 15 mg Cetirizine. The patient received simoctocog alfa from 30-Jan-2012 to 06-Aug-2012 in this study. No further allergic oedema or other potentially allergic type reactions were reported for this patient during the remaining study period, and also not during the extension study (GENA-13) so far indicating that this was not an allergic reaction to simoctocog alfa.

11.1.3.5.1.1. Clinical evaluator's comment

The sponsor's response is satisfactory.

11.1.3.6. Question 6

Please comment on potential hypersensitivity and allergic reactions to simoctocog alfa identified in the total safety population (all five studies) and in the paediatric population (GENA-03). Have any analyses of the safety data been undertaken using MedDRA search criteria for "hypersensitivity" (SMQ), "anaphylactic reactions" (SMQ), or "allergic conditions" (HLGT)?

11.1.3.6.1. Sponsor's response (complete)

Tables Australia_SAF.6.1 through to 6.5 display results of MedDRA search criteria for "anaphylactic reactions (SMQ)", "hypersensitivity reactions (SMQ)", both using narrow term and broad term criteria, and "allergic reactions (HLGT)" of the GENA-03 study, while Tables Australia_SAF.6.6 through to 6.10 show the corresponding results for the studies GENA-01, GENA-08, and GENA-09. All 18 subjects included in GENA04 were previously treated in GENA09. No TEAEs according to the above definition were reported in GENA04 (refer to Table Australia_SAF6.1, Australia_SAF6.2, Australia_SAF6.3, Australia_SAF6.4, Australia_SAF6.5, Australia_SAF6.6, Australia_SAF6.7, Australia_SAF6.8, Australia_SAF6.9, Australia_SAF6.10).

All these adverse events were considered "not related" by the investigator. Please refer also to our responses to Safety questions no. 2 (rashes in GENA-01 and GENA-03), no. 3 (chills in GENA-03), no. 4 (pruritus in GENA-01 and GENA-03) and no. 5 (allergic oedema in GENA-03).

From the Applicants point of view there is no increased risk of potential hypersensitivity and allergic reactions to simoctocog alfa in the safety population.

All supportive documents are included in Module 1.0.2 "Supportive clinical listings and tables".

11.1.3.6.1.1. Clinical evaluator's comment

The sponsor's response is satisfactory. The tables referred to in the response have been examined. In GENA-03 (n=59), 8 (13.6%) subjects experienced a TEAE classified as SMQ Hypersensitivity (broad): 4 (6.8%) for rash; 1 (1.7%) for each of allergic oedema, asthma, conjunctivitis allergic, pruritus, and rhinitis allergic. In GENA-01, GENA-08, and GENA-09, 4 (5.3%) subjects out of a total of 76 experienced a TEAE classified SMQ Hypersensitivity (broad): 1 each for oropharyngeal spasm, pruritus, rash and seasonal allergy. No anaphylactic reactions (narrow definition) were reported in any of the studies, while 1 patient in GENA-03 was reported with two TEAEs considered to be SMQ anaphylactic reaction (broad definition) (1 x cough, 1 x rash). Overall, the available data suggest that hypersensitivity / allergic reactions do not appear to be a significant clinical problem with simoctocog alfa.

Table 60: Degree of haemorrhage

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

In Section 2.7.3.4 (Analysis of Clinical Information Relevant to Dosing Recommendations) of the Clinical Summary (2.7), the sponsor noted that the dosing recommendations for the simoctocog

alfa studies, except GENA-09, were higher than the dosing recommendations in the EMEA *Core SPC for Human Plasma-Derived and Recombinant Coagulation Factors FVIII Products, CPMP/BPWG/1619/99, London, 29 June 2000.* The dosing recommendations for on-demand bleeding in the EMEA 2000 document are identical to those being recommended by the sponsor provided above in Table 60. It is noted that the EMA 2000 document has been superseded by the 2012 document, *EMA Guideline on core SmPC for human plasma derived a recombinant coagulant factor VIII products, EMA/CHMP/BPWP/1619/1999 rev.1, 24 May 2012)*. The dosing recommendations for on-demand treatment of bleeding episodes in both EMA documents are the same. However, neither of the two EMA guidance documents have been adopted by the TGA, presumably because they relate specifically to the content and format of the European prescribing information (that is, the SmPC).

The sponsor comments that, as almost 50% of the bleeding events in the studies were moderate to major, the average actual doses administered in the studies are in line with the EMA recommendations in the 2000 document. The sponsor comments that the proposed dosing scheme was validated by the results obtained for incremental recovery of FVIII in each of the studies. The IVR in the ITT population increased approximately 2% per IU/kg dose of simoctocog alfa across each of the studies. Consequently, it can be predicted that an increase in FVIII of x% will be achieved with x/2 IU/kg of simoctocog alfa (for example, 20% to 40% increase in FVIII will be achieved with simoctocog alfa 10 IU/kg to 20 IU/kg). In addition, the PK data from study GENA-01 showed that simoctocog alfa and full-length rFVIII BHKwere bioequivalent as regards AUCnorm (h•IU/mL/[IU/kg], and that the PK parameters were similar for the two products. Consequently, the approved dosage recommendations for full-length rFVIII BHKcan be reasonably applied to those proposed for simoctocog alfa.

11.1.3.7. Question 7

Dosage and Administration (Surgical prophylaxis) - The proposed dosage regimens being proposed for surgery differ from those used in all five clinical studies. In particular, no preoperative dose is being proposed for minor surgical procedures (including tooth extraction) although a preoperative loading dose was recommended for all minor surgical procedures (including tooth extraction). Why do the proposed dosing regimens for surgical prophylaxis differ from those used in the five clinical studies?

11.1.3.7.1. Sponsor's response (complete)

The dosing information is based on the European core SmPC (already approved by EMA) and in order to harmonise dose recommendations worldwide we propose to keep these dosing recommendations also for Australia. Thus with regard to surgeries, only the target plasma level is recommended.

11.1.3.7.1.1. Clinical evaluator's comment

The sponsor's response is acceptable.

The sponsor's proposed dosage regimens for the on-demand treatment of bleeding episodes are summarised below in Table 61 (adapted from proposed PI). The required factor VIII levels proposed by the sponsor surgery are consistent with the levels specified in the PI of a full-length rFVIII. However, in the *Australian Health Minister's Advisory Council (AHDCO), Evidence-based clinical practice guideline for the use of recombinant and plasma-derived FVIII and FIX products, Released June 2006 (National Blood Authority)* the peak post-infusion levels for rFVIII for minor surgery are 60-80 IU/dL and pre- and post-infusion levels for rFVIII for major surgery are 80-100 IU/dL.

Table 61: Type of surgical procedure

Surgical procedure	FVIII level required (IU/kg)	Frequency of doses (hours) and duration of therapy (days)
Minor (incl. tooth extraction)	30 to 60%	Every 24 hours, at least 1 day, until healing is achieved.
Major	80 to 100% (pre- and post-operative)	Repeat infusion every 8 to 24 hours until adequate wound healing, then therapy for at least another 7 days to maintain FVIII activity of 30 to 60% (IU/dL).

FVIII = coagulation factor VIII; IU = international units.

The sponsor's proposed levels are identical to those provided in the EMA guidance documents (2000 and 2012) for the SmPC for rFVIII products. In Section 2.7.3.4 (Analysis of Clinical Information Relevant to Dosing Recommendations) of the Clinical Summary (2.7), the sponsor noted that nearly all 35% of the surgeries were major and that the average actual doses administered were in line with the EMEA (2000) recommendations. For surgical prophylaxis, the dosage and duration of treatment with simoctocog alfa depended on the type of surgery and the patient's individual IVR. The required dosage was determined using the following formula:

Dose = target increase of FVIII (IU/dL) * body weight/actual IVR (IU/dL)/(IU/kg).

12. Second round benefit-risk assessment

12.1. Second round assessment of benefits

After consideration of the sponsor's responses to the clinical questions raised following the first round evaluation, the benefits of simoctocog alfa remain unchanged from those identified in the First round.

12.2. Second round assessment of risks

After consideration of the sponsor's responses to the clinical questions raised following the first round evaluation, the risks of simoctocog alfa remain unchanged from those identified in the First round.

12.3. Second round assessment of benefit-risk balance

The benefit-risk balance for simoctocog alfa for the proposed indications is considered to be favourable for patients with severe haemophilia A in adults and children aged 2 years and older.

13. Second round recommendation regarding authorisation

It is recommended that NUWIQ be approved for the "treatment and prophylaxis of bleeding (also during and after surgery) in previously treated paediatric (≥ 2 years) and adult patients

with severe haemophilia A (congenital factor VIII deficiency)".

The indication recommended for authorisation includes reference to severe haemophilia A. The indication proposed by the sponsor excludes the reference to severe haemophilia A.

14. References

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