Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Simoctocog alfa *rhu*

Proprietary Product Name: Nuwiq

Sponsor: Octapharma Australia Pty Ltd

June 2016

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 <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
ABR	Annualised bleeding rate
ADR	Adverse drug reaction
AE	Adverse event
ASA	Australian-specific annex
ACSOM	Advisory Committee on the Safety of Medicines
AUC	Area under the curve (from baseline to infinity)
AUC_{norm}	Area under the curve normalised to the dose administered
BDD	B-domain-deleted
BLEED	Study population of bleeds treated with simoctocog alfa
BU	Bethesda units
CER	Clinical evaluation report
CHMP	Committee for Medicinal Products for Human Use
CHR	Chromogenic
CI	Confidence interval
CL	Clearance
C_{max}	Maximum plasma concentration
CMI	Consumer Medicine Information
DNA	Deoxyribonucleic acid
ED	Exposure day
EMA	European Medicines Agency
EU	European Union
FFP	Fresh frozen plasma
FVIII	Coagulation FVIII
FVIII:C	FVIII coagulant activity

Abbreviation	Meaning
GCP	Good clinical practice
HLGT	High-level group term
HIV	Human immunodeficiency virus
HJHS	Haemophilia Joint Health Score
HmA	Haemophilia A
ICH	International Committee for Harmonization
IDMC	Independent Data Monitoring Committee
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
OLSS	Office of Laboratories and Scientific Services
OS	One-stage
pdFVIII	Plasma-derived coagulation FVIII
PI	Product Information
PIP	Paediatric Investigational Plan
PK	Pharmacokinetic
PP	Per-protocol
PROPH	Study population of patients receiving prophylaxis with simoctocog alfa
PTP	Previously treated patient
PUP	Previously untreated patient
rFVIII	Recombinant coagulation FVIII

Abbreviation	Meaning
RMP	Risk management plan
SAE	Serious adverse event
SD	Standard deviation
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA queries
SOC	System organ class
SURG	Study population of surgeries treated with simoctocog alfa
$t_{1/2}$	Half-life
TGA	Therapeutic Goods Administration
TKR	Total knee replacement
vWD	Von Willebrand's disease
vWF	Von Willebrand factor

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Decision:	Approved
Date of decision:	5 November 2014
Active ingredient(s):	Simoctocog alfa *rhu*
Product name(s):	Nuwiq
Sponsor's name and address:	Octapharma Australia Pty Ltd Jones Bay Wharf, Suite 42/26-32 Pirrama Rd Pyrmont, NSW 2009
Dose form(s):	Powder for Injection
Strength(s):	250IU, 500IU, 1000IU, 2000IU
Container(s):	Glass Type I Clear
Pack size(s):	1 vial of Nuwiq and 1 vial of pre-filled syringe containing 2.5mL of sterile water
Approved therapeutic use:	*Treatment and prophylaxis of bleeding (also during and after surgery) in previously treated paediatric (≥ 2 years) and adult patients with haemophilia A (congenital FVIII deficiency).* *Nuwiq does not contain von Willebrand factor and is thus not indicated to treat von Willebrand's disease.*
Route(s) of administration:	Intravenous (IV)
Dosage:	The dose and duration of the substitution therapy depend on the severity of the FVIII deficiency, on the location and extent of the bleeding, and on the patient's clinical condition. See Attachment 1 Product information for further details.
ARTG number (s):	213938, 213939, 213940 and 213941

Product background

This AusPAR describes the application by the sponsor, Octapharma Australia Pty Ltd, to register a new chemical entity, simoctocog alfa as Nuwiq. Nuwiq was initially proposed to be used for

> *Treatment and prophylaxis of bleeding (also during and after surgery) in patients with haemophilia A (congenital FVIII 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 of all ages, including newborns.

During the TGA's evaluation process the proposed indication was modified to

Treatment and prophylaxis of bleeding (also during and after surgery) in previously treated paediatric (≥ 2 years) and adult patients with haemophilia A (congenital FVIII deficiency).

Haemophilia A is an inherited sex-linked disorder of blood coagulation in which affected males do not produce functional coagulation Factor VIII (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 (FVIII:C [% 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 bleed. Most bleeds occur in joints and muscles. Without adequate treatment these repeated haemarthroses and haematomas lead to long-term sequelae with severe disability. 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. Therapy rests on FVIII replacement.

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.

The mechanism of action of simoctocog alfa is replacement, that is, correction of the FVIII level. Simoctocog alfa is a B-domain deleted (BDD) recombinant human coagulation FVIII (rFVIII) derived from the human embryonic kidney 293F cell line.

Australian clinical guidelines for treatment include:

1. Evidence-based clinical practice guidelines for the use of recombinant and plasma-derived FVIII and FIX products (NBA/AHCDO, 2006).

The current European Union (EU) guideline relevant to this application[4] was adopted by the TGA on 1 June 2014, during the evaluation process for this application. Generally the sponsor's dataset met the requirements of the new guideline.

Currently registered products in Australia are listed below (Table 1).

[1] Tuddenham EGD, Kannicht C, Agerkvist I, Sandberg H, Knaub S, Zozulya N. From human to humans - Introducing the first recombinant human FVIII product produced from a human cell line. Thromb Haemost Suppl 2010; 103: 4-14.
[2] Coppola A, Di Capua M, Di Minno MND, Di Palo M, Marrone E, Ieranò P, et al. Treatment of hemophilia: a review of current advances and ongoing issues. J Blood Med 2010; 1: 183-195.
[3] Lee M, Morfini M, Schulman S, and Ingerslev J. The Design and Analysis of Pharmacokinetic Studies of Coagulation Factors (Subcommittee on FVIII and Factor IX of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis). 21-Mar-2001.
[4] *Guideline on the clinical investigation of recombinant and human plasma-derived FVIII products (EMEA/CHMP/BPWP/144533/2009)*
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500109692.pdf

Table 1: Currently registered products in Australia

Product	Approved indication
Plasma-derived	
Biostate and Aleviate	The treatment of bleeding episodes including surgical bleeding in patients with von Willebrand disease when desmopressin (DDAVP) treatment is ineffective or contraindicated The treatment and prophylaxis of bleeding associated with FVIII deficiency due to haemophilia A.
Octanate	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital FVIII deficiency). This preparation does not contain von Willebrand factor in pharmacologically effective quantities and is therefore not indicated in von Willebrand's disease.
Wilate	*Von Willebrand disease (VWD)* Treatment of bleeding episodes including surgical bleeding in patients with von Willebrand's disease when desmopressin treatment is ineffective or contraindicated. *Haemophilia A* Treatment and prophylaxis of bleeding including surgical bleeding in patients with haemophilia A (congenital FVIII deficiency). Controlled clinical trials to evaluate the safety and efficacy of WILATE® in major surgeries are ongoing in both VWD and haemophilia A patients. Therefore, limited data are presently available on which to evaluate or to base dosing recommendations in either of these settings. Thus, in the case of major surgical interventions, a precise monitoring of the substitution therapy by means of coagulation analysis (FVIII:C and possibly vWF:RCo) is indispensable. There are insufficient data to recommend the use of WILATE® in children less than 12 years of age.
Recombinant	
Increasing generation reflects theoretically less exposure to proteins other than rhFVIII[5].	First generation. CHO cell line, i.e. hamster. RECOMBINATE is indicated for use in haemophilia A (classical haemophilia) for the prevention and control of haemorrhagic episodes. Patients with haemophilia A may be treated with RECOMBINATE as perioperative management. RECOMBINATE is not indicated in von Willebrand's disease.

[5] http://www.uptodate.com/contents/treatment-of-hemophilia?source=machineLearning&search=factor+viii+concentrates&selectedTitle=5%7E20&sectionRank=1&anchor=H9#H9

Product	Approved indication
Octocog alfa (Recombinate)	
Octocog alfa (Kogenate FS) (Helixate NexGen)	Second generation. Full length FVIII. Baby hamster kidney (BHK) cell line. KOGENATE FS is indicated for the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital FVIII deficiency). It may also be used in patients with FVIII inhibitors (neutralising antibodies) who continue to respond to infused FVIII. KOGENATE FS does not contain von Willebrand Factor and hence is not indicated in von Willebrand's disease.
Octocog alfa (Advate)	Third generation. Full length FVIII. CHO cell line. ADVATE is indicated for use in haemophilia A for prevention and control of haemorrhagic episodes. Patients with haemophilia A may be treated with ADVATE as perioperative management. ADVATE is not indicated in von Willebrand's disease.
Moroctocog alfa (Xyntha)	Third generation. B-domain deleted. CHO cell line. XYNTHA is indicated for the control and prevention of haemorrhagic episodes in patients with haemophilia A, including control and prevention of bleeding in surgical settings. XYNTHA does not contain von Willebrand factor and should not be used by patients with von Willebrand's disease.
Turoctocog alfa (NovoEight)	Third generation. Truncated B domain. CHO cell line. NovoEight is indicated for the treatment and prophylaxis of bleeding episodes in patients with haemophilia A, including control and prevention of bleeding in surgical settings.
Efraloctocog alfa (Eloctate)	Long-acting via Fc-moiety. B-domain deleted. HEK cell line. ELOCTATE is a long-acting antihaemophilic factor (recombinant) indicated in adults and children (≥12 years) with haemophilia A (congenital FVIII deficiency) for: Control and prevention of bleeding episodes. Routine prophylaxis to prevent or reduce the frequency of bleeding episodes. Perioperative management (surgical prophylaxis). ELOCTATE does not contain von Willebrand factor, and therefore is not indicated in patients with von Willebrand's disease.
Other	

Product	Approved indication
Feiba-NF	A complex of coagulation factors; for use in patients with inhibitors. FEIBA-NF is indicated for routine prophylaxis, control of spontaneous bleeding episodes and use in surgery in haemophilia A or B patients with inhibitors.

Trade names of comparator products have been replaced by general terms in this AusPAR and in Attachment 2 Extract from the CER.

Regulatory status

This is an application for a new biological entity for Australian regulatory purposes.

Simoctocog alfa was granted a European Commission marketing authorisation in July 2014 and was approved in Canada in November 2014 (Table 2). Simoctocog alfa has not been approved in the USA, Switzerland or New Zealand.

Table 2: International regulatory status

Country	Trade name	Approval date	Approved indications
Centralised procedure in EU including Norway, Liechtenstein, Iceland	Nuwiq	July 2014	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital FVIII deficiency). Nuwiq can be used for all age groups.
Canada	Nuwiq	November 2014	Treatment and prophylaxis of bleeding in patients of all ages suffering with haemophilia A (congenital FVIII deficiency).

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

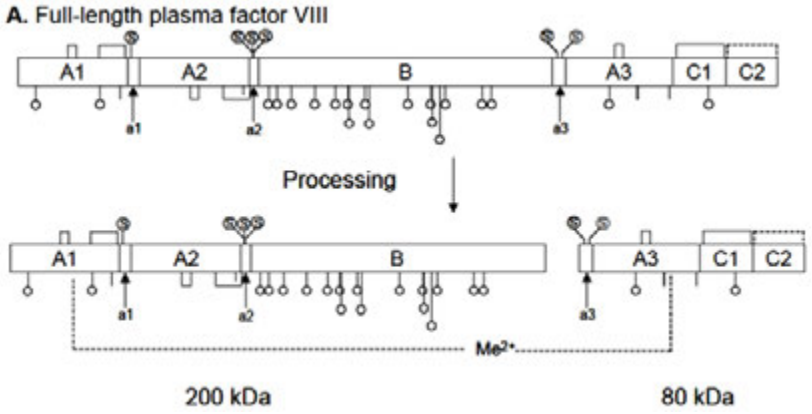
II. Quality findings

Drug substance (active ingredient)

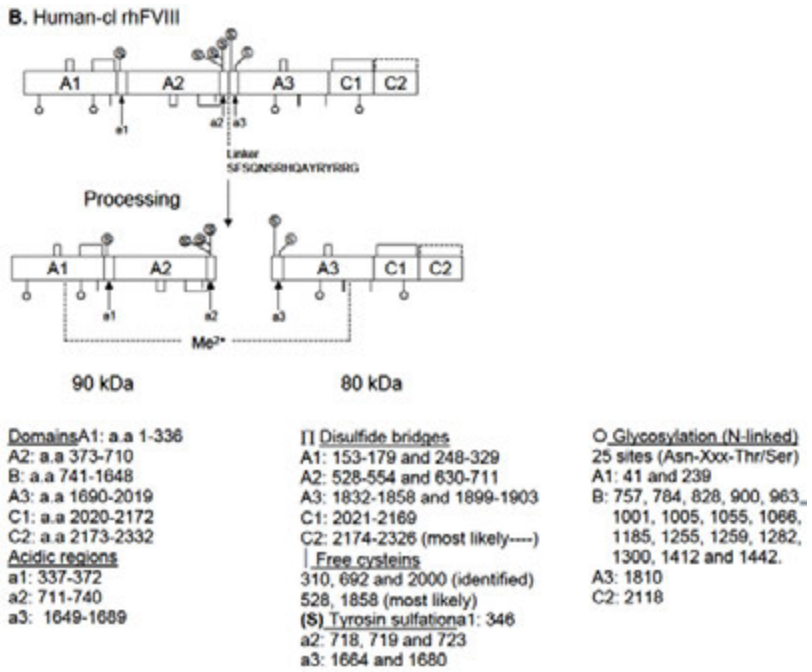
Octapharma's human cell line recombinant FVIII (Human-cl rhFVIII, simoctocog alfa) is a glycoprotein with an approximate molecular mass of 170 kilo Daltons (kDa), comprising the FVIII domains A1-A2 + A3-C1-C2 with the B-domain, present in the full-length plasma-derived FVIII (pdFVIII) deleted. Simoctocog alfa consists of 1440 amino acids. A linker sequence consisting of 16 amino acids was inserted in the 170 kDa single chain molecule of simoctocog alfa between the A2 and A3 domain in order to replace the B-domain. The first eight amino acids in the N-terminal part of the linker correspond to the first eight amino acids from the FVIII B-domain, while the remaining arginine-rich octapeptide was chosen to provide a recognition site for furin or furin-like proteases in order to ensure similar proteolytic processing as for the full-length FVIII molecule. Figure 1 below describes the structure of human FVIII.

Figure 1: Schematic structures

A: Full-length FVIII



B: Simoctocog alfa



Potential sites in simoctocog alfa for N-linked glycosylation, tyrosine sulfation, disulphide bridges, free cysteines and regions rich in acidic amino acids are shown in comparison with full-length FVIII.

Cell banking processes are satisfactory.

All viral/prion safety issues have been addressed, including use of animal-derived excipients, supplements in the fermentation process and in cell banking.

Physical and chemical properties

Simoctocog alfa drug substance is a clear, colourless solution with a pH ranging between 6.7 and 7.2. A report provided showed physico-chemical consistency of the process validation batches of the drug substance. Characterisation of batches used in toxicological studies and of batches used in early clinical development in 2008 was also provided for comparison.

Overall, the physical and chemical characterisation of simoctocog alfa from process validation batches showed that the main structural features of this protein were those expected for a BDD FVIII protein and thus very close to those of B-domain-less pdFVIII. The glycosylation pattern was clearly mapped, and the antigenic Gal-α1-3βGalβ1-(3)4GlcNAc-R (α-Gal) epitope as well as N-glycolylneuraminic acid was absent. For the clinical batches however, it was noted that N-acetylneuraminic acid was the only sialic acid present.

Appropriate validation data have been submitted in support of the specification test procedures.

Drug product

Simoctocog alfa drug product is a white sterile lyophilised powder and solvent for solution for injection. The lyophilised powder is supplied in single dose vials containing 250 international units (IU), 500 IU, 1000 IU, and 2000 IU of recombinant FVIII per vial. Before use, the lyophilised powder is reconstituted with a single dose solvent pre-filled syringe containing 2.5 mL of sterilised water for injections. The reconstituted solution is described as a clear, colourless solution, free from visible particles, containing 100 IU/200 IU/400 IU/800 IU FVIII:C/mL. The concentration of each of the excipients is the same for all strengths, only the recombinant FVIII concentration varies.

Stability

Expected shelf life is 24 months at +2°C to +8°C when protected from light.

Note: considering the data provided (especially on the commercial batches, Stability Study report OC13-0068), excursion outside of this condition is not permitted. The recommended maximum storage time as reconstituted drug product is 3 hours.

Biopharmaceutics

Biopharmaceutic data are not required for this product because it is not a biosimilar product.

Quality summary and conclusions

The administrative, product usage, chemical, pharmaceutical, microbiological data submitted in support of this application have been evaluated in accordance with the

Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

There are no outstanding issues and the quality evaluator(s) recommend that Nuwiq (Human cell line recombinant human FVIII (Human-cl rhFVIII), simoctocog alfa), 2000IU/1000IU/500IU/250IU, powder and solvent for solution for injection be approved.

Conditions of Registration

Batch Release Testing

It is a condition of registration that, as a minimum, the first five independent batches of

- Nuwiq Human cell line recombinant human FVIII (Human-cl rhFVIII), 2000 IU, powder and solvent for solution for injection
- Nuwiq Human cell line recombinant human FVIII (Human-cl rhFVIII), 1000 IU, powder and solvent for solution for injection
- Nuwiq Human cell line recombinant human FVIII (Human-cl rhFVIII), 250 IU, powder and solvent for solution for injection
- Nuwiq Human cell line recombinant human FVIII (Human-cl rhFVIII), 500 IU, powder and solvent for solution for injection

imported into/manufactured in Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Office of Laboratories and Scientific Services (OLSS).

III. Nonclinical findings

Introduction

A limited data package was submitted and consisted of one combined pharmacology/ pharmacokinetics (PK) study in a dog model of haemophilia A, one single dose toxicity and two repeat dose toxicity studies in monkeys, one local tolerance study and four (4) immunogenicity studies. In addition, in vitro pharmacology studies were provided. The single and repeat-dose toxicity studies and the local tolerance study were conducted according to Good Laboratory Practice (GLP) principles, with the key repeat-dose studies in Cynomolgus monkeys lacking toxicokinetics. Systemic exposure to simoctocog alfa in these studies would likely be comprehensive given administration was by intravenous (IV) injection/infusion.

Administration of simoctocog alfa followed treatment regimens covering haemorrhagic events and its use in surgery under on-demand conditions or in prophylaxis. Dose is calculated using the formula:

> Required units (IU) = body weight (kg) x desired FVIII rise (% or IU/dL) x 0.5 (IU/kg per IU/dL)

Dosing for categories (shown below in table) of use varied but it was recommended that not more than 4 mL/minute be administered.

Degree of haemorrhage/ Type of surgical procedure	FVIII 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 hrs. At least 1 day, until bleeding episode as indicated by pain is resolved of healing is achieved.
More extensive haemarthrosis, muscle bleeding or haematoma.	30-60	Repeat infusion every 12 to 24 hrs 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 hrs until threat is resolved.
Surgery		
Minor surgery including tooth extraction.	30-60	Every 24 hrs, at least 1 day, until healing is achieved.
Major surgery.	80-100 pre- and post-operative.	Repeat infusion every 8-24 hrs until adequate wound healing, then therapy for at least another 7 days to maintain a FVIII activity of 30% to 60% (IU/dL).

For long-term prophylaxis in patients with severe haemophilia A, the usual doses are 20 to 40 IU of FVIII per kg body weight at intervals of 2 to 3 days. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

Pharmacology

Primary pharmacology

The biological activity of simoctocog alfa was demonstrated in in vitro assays and in a dog model of haemophilia A.

In vitro data indicated that simoctocog alfa has comparable FVIII activity with other rFVIII or pdFVIII using a two-stage chromogenic assay and a one stage (OS) assay. The effect on FVIII activity of simoctocog alfa by thrombin was similar to human pdFVIII. The interaction of simoctocog alfa with thrombin is similar to that of pdFVIII. Simoctocog alfa exhibits a similar pattern of Factor Xa (FXa) generation as other rFVIII and pdFVIII products. Studies also showed that simoctocog alfa has the expected interaction with human Protein C for a FVIII protein; inactivation of simoctocog alfa by activated Protein C was similar to the inactivation of other rFVIII. Simoctocog alfa displays similar affinity for von Willebrand factor (vWF) to a BDD rFVIII comparator but higher affinity than full-length rFVIII products. It has a higher binding capacity than any of the FVIII comparator

proteins; the capacity was 10 to 20 % higher than for a BDD rFVIII comparator and 30 to 40% higher than for full-length rFVIII, suggesting that simoctocog alfa may have a better stability profile in patients than other rFVIII products.

A pharmacological assessment of simoctocog alfa, in comparison to another BDD rFVIII product, in two dogs with haemophilia A showed cuticle bleeding time (CBT) was reduced by both agents. Neither treatment resulted in a shortening of activated partial thromboplastin time (APTT) and whole blood clotting time. The dog study gave very limited evidence of potential efficacy in haemophilia A patients, although in vitro data demonstrated comparable activities with human derived or other recombinant FVIII products.

There were no secondary or safety pharmacology studies for simoctocog alfa. This is acceptable given the extensive clinical experience with rFVIII products and the absence of adverse effects (including electrocardiogram (ECG)) in the repeat dose toxicity studies in monkeys at IV doses up to 500 IU/kg, which is 9 to 10 times the clinical exposure based on dose (IU/kg), peak plasma concentration (C_{max}) and area under the plasma concentration versus time curve (AUC).

Pharmacokinetics

Pharmacokinetic data were generated from two (2) dogs (with haemophilia A) in the pharmacology study and Cynomolgus monkeys in the toxicity studies. The limited pharmacokinetic data showed comparable PK profiles for simoctocog alfa and a BDD rFVIII comparator CHO in haemophilia A dogs at 125 IU/kg, with clearance of 5 to 6 mL/h/kg and half-life ($t_{1/2}$) of 7 to 9 h. Similar pharmacokinetic profiles were seen in monkeys at 500 IU/kg but slower clearance (CL) (3 to 4 mL/h/kg) and longer elimination $t_{1/2}$ (10 to 11 h) at a lower dose (50 IU/kg), comparable to those in patients (CL 2.94 mg/h/kg, $t_{1/2}$ 14.7 h). Repeated dosing in monkeys resulted in lower plasma FVIII levels due to the development of anti-FVIII antibodies, which is common when testing recombinant human anticoagulant factors in animal species.

Toxicology

Acute toxicity

A single-dose toxicity study was conducted in the rat at one dose level of 10000 IU/kg IV. There were no clinical signs of toxicity, bodyweight gain was normal and all animals survived to terminal sacrifice. Gross pathology findings were limited to one male with a pale liver and a female had congestion of the spleen and pale kidneys (findings considered to be of doubtful relevance to treatment). The dose in rats was 200 fold higher than the recommended maximum clinical dose of 50 IU/kg. Simoctocog alfa has low potential for acute toxic effects.

Repeat-dose toxicity

There were two repeat-dose IV toxicity studies both in Cynomolgus monkeys; one pivotal 4 week study and one pilot dose range-finding study. Both studies were conducted according to GLP principles and included recovery periods of 2 weeks. The 4 week pivotal study included a comparator group dosed with a pdFVIII product pdFVIII.

The only treatment-related findings in the repeat dose toxicity studies were decreased blood coagulation times, APTT values, a pharmacological effect of simoctocog alfa, after the first dose and then, after repeated dosing, prolonged coagulation times and bruising on the groin, face and injection site in the high dose simoctocog alfa group (500 IU/kg/day)

due to the neutralisation of endogenous FVIII by anti-VIII antibodies. The findings were similar in simoctocog alfa and pdFVIII treated animals except for higher anti-FVIII antibody titres in the simoctocog alfa group than in the pdFVIII group and the absence of bruising in the pdFVIII group. In the 4 week study, one female given 500 IU/kg simoctocog alfa was sacrificed on day 30 due to poor condition, internal bleeding, low red blood cell count (RBC), haemoglobin and haematocrit values and pale organs; this animal had very high levels (>2 times other animals) of anti-FVIII antibodies.

Plasma FVIII concentrations were measured in the pivotal toxicity study only at one time point after dosing on several days. High anti-FVIII antibodies were present in animals treated with 500 IU/kg simoctocog alfa and pdFVIII from Day 13 and resulted in low plasma FVIII activities (below baseline values) after repeated dosing and after the recovery period. The low dose (50 IU/kg) of simoctocog alfa induced low levels of antibodies, maintaining plasma FVIII levels slightly above the baseline values in males and slightly below baseline values in females after 3 weeks of dosing. Exposures (based on C_{max} and AUC) at the high dose (500 IU/kg) were 9 to 10 fold higher than the clinical exposure in haemophilia A patients with prophylactic therapy (see table below).

Table 3: Exposures in repeat-dose toxicity studies compared with the clinical exposure

Species	Dose IU/kg	C_{max} IU/mL *	AUC IU.h/mL #	Animal/human exposure ratio	
				C_{max}	AUC‡
Monkey Cynomolgus)	50	3.41	11.4	2.3	1.2
	500	12.59	95.3	8.6	9.9
Human Study GENA-01†	~58	1.46	22.5	–	–

* Mean values of male and female monkeys (4/sex/dose level) 15 min after the first dose in the 4-week study. # Values from the pilot study in 2 monkeys (one/sex/dose level); $AUC_{0\text{-}24h}$ for monkeys and $AUC_{0\text{-}\infty}$ for humans. † Data in adolescent and adults (lower AUC and C_{max} values were observed in children). ‡ Based on weekly exposure for prophylaxis (every 2-3 days), ratio = monkey AUCx7/human AUCx3.

Genotoxicity and carcinogenicity

No genotoxicity or carcinogenicity studies were included in this submission. This omission is acceptable in accordance with the TGA adopted EU guideline.[6] Standard carcinogenicity assays of biotechnology-derived pharmaceuticals are generally inappropriate; the immunogenicity of rFVIII in experimental species would not allow for carcinogenicity study of adequate duration. As a large protein the drug is not expected to interact directly with deoxyribonucleic acid (DNA) or other chromosomal material. No causes for concern of a genotoxic nature have been identified for rFVIII products. rFVIII has been used for years in haemophilia A patients, and there are no mechanistic data to suggest a mutagenic or proliferative potential for simoctocog alfa.

[6] CPMP/ICH/302/95 Note for Guideline on Preclinical Safety Evaluation of Biotechnology Derived Pharmaceuticals. http://www.tga.gov.au/pdf.euguide/ich030295en.pdf

Reproductive toxicity

No reproductive toxicity studies were conducted with simoctocog alfa. The absence of reproductive toxicity studies is appropriate given that the product is only intended for physiological replacement of normal FVIII activity and that haemophilia A is a sex-linked disease that effectively only occurs in males. No effects on the reproductive organs were seen in histopathology assessment of reproductive organs in the 4 week repeat dose toxicity study in male and female monkeys. rFVIII has been used in haemophilia A patients for years and there is no evidence of adverse effects on fertility or embryofoetal development.

Pregnancy classification

The sponsor has not proposed Pregnancy Category. A Pregnancy Category of B2[7] has been assigned to other rFVIII replacement product/s and this category is considered appropriate for simoctocog alfa.

Local tolerance

An investigation into the effect of simoctocog alfa on local tolerance in rabbits (New Zealand (NZ) White) following perivenous injection was submitted. A single perivenous dose (0.2 mL) of simoctocog alfa (200 IU/mL) was well tolerated with oedema, isolated cases of minimal haemorrhage, slight scab and minimal dermal inflammation observed in both the control ear and treatment ear. Although the excipients used in the test formulation differ from the clinical formulation (trehalose and histidine in the test formulation instead of sucrose and arginine), these excipients are not expected to cause significant adverse effects at the injection site. The simoctocog alfa formulation is expected to be well tolerated by patients.

Immunogenicity

As discussed above, simoctocog alfa was immunogenic in monkeys and induced neutralising anti-FVIII antibodies after repeated dosing, resulting in low plasma FVIII activities and bleeding.

Immunogenicity of simoctocog alfa was also assessed using an in vitro T cell[8] assay (EpiScreen™) using T cells from a panel of human donors. The assay was used to determine helper CD4+ T cell[9] responses to the test agent and thus potential immunogenicity in vivo. Assessment of T cell responses in the presence of vWF found that vWF reduced the immunogenicity of FVIII. Without vWF, simoctocog alfa gave a positive response in 28% donors in the T cell proliferation assay and 26% in the interleukin 2 (IL-2) secretion assay (ELISpot assay), with high correlation between the two assay results, compared to only 6% and 8%, respectively, for the human plasma derived FVIII. The response rate was reduced to 12% and 10%, respectively, in the presence of vWF. The findings suggest that simoctocog alfa is likely to be more immunogenic than human plasma derived FVIII but the endogenous vWF reduces the immunogenicity of simoctocog alfa. Also studied for their effect on immunogenic potential (using the EpiScreen assay) were three simoctocog alfa isoforms, with response rates (6 to 10%) similar to the above study. Overall, the in vitro results suggest a low risk of immunogenicity in humans.

[7] Category B2. Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.
[8] T cell: A type of white blood cell that is of key importance to the immune system and is at the core of adaptive immunity, the system that tailors the body's immune response to specific pathogens.
[9] Mature T helper (T_h) cells express the surface protein CD4 and are referred to as $CD4^+$ T cells.

Paediatric use

Simoctocog alfa is proposed for paediatric use and no specific studies in juvenile animals were submitted. The dosage is the same in adults and children, however, shorter dosage intervals or higher doses may be necessary for children. The sponsor stated that the pharmacokinetics, safety and efficacy of simoctocog alfa in previously treated children below the age of 13 had been established. Data has been obtained in 29 children between 2 and 5 years of age and 30 children between 6 and 12 years of age. Half-life and recovery are slightly less in children than in adults and CL is slightly higher. Efficacy in prophylaxis and the treatment of bleeds is comparable between children and adults.

Juvenile animal studies are not considered essential for simoctocog alfa considering the long history of clinical use of recombinant human FVIII products, therapeutic indication of the drug and availability of clinical data in paediatric patients.

Nonclinical summary and conclusions

- Limited studies were presented in this application but were sufficient to demonstrate the pharmacological properties and identify potential toxicity in patients.
- Pharmacology studies (in vivo and in vitro) were available for assessment. In vitro studies with a range of simoctocog alfa batches and marketed FVIII products showed comparable FVIII activity. The effect on FVIII activity of simoctocog alfa by thrombin showed that it has good sensitivity for activation with thrombin and that it behaves similarly to human pdFVIII in this respect. Simoctocog alfa exhibits a similar pattern of Factor Xa (FXa)[10] generation as other FVIII products, both plasma-derived and recombinant. Studies also showed that simoctocog alfa has the expected interaction with human Protein C for a FVIII protein. Simoctocog alfa showed a higher vWF binding capacity than any of the FVIII comparator proteins, suggesting that simoctocog alfa may have a better stability profile in patients than other rFVIII products (full length and BDD). A small in vivo study in two dogs with haemophilia A showed reduced cuticle bleeding times by simoctocog alfa and a BDD rFVIII comparator.
- No dedicated safety or secondary pharmacology studies were submitted. This is acceptable given the extensive clinical experience with rFVIII products and the absence of adverse effects (including ECG) in the repeat dose toxicity studies in monkeys at IV doses up to 500 IU/kg, which is 9 to 10 times the clinical exposure based on dose (IU/kg), C_{max} and AUC.
- PK data were generated in dogs (with haemophilia A) and Cynomolgus monkeys. The limited pharmacokinetic data in haemophilia A dogs showed comparable PK profiles for simoctocog alfa and a BDD rFVIII CHO. In Cynomolgus monkeys given a bolus IV injection of 50 IU/kg simoctocog alfa, values for CL and elimination $t_{1/2}$ were similar to those in patients. Repeated dosing in monkeys resulted in lower plasma FVIII levels due to the development of anti-FVIII antibodies, which is common when testing recombinant human coagulant factors in animal species.
- A single-dose toxicity study in rats showed no overt signs of treatment-related toxicity at the highest single IV dose of 10000 IU/kg.
- In two repeat-dose toxicity studies in monkeys, simoctocog alfa was administered IV to Cynomolgus monkeys; recovery periods were included in both studies. Human pdFVIII was used as a comparator. Simoctocog alfa was well tolerated by Cynomolgus monkeys, with the only drug-related effects being shortened APTT after the first dose.

[10] Factor X, also known by the eponym Stuart–Prower factor or as prothrombinase, thrombokinase or thromboplastin, is an enzyme of the coagulation cascade. It is a serine endopeptidase.

However, bruising, haemorrhage and prolonged APTT were observed after repeated dosing at 500 IU/kg (9 to 10 times the clinical exposure based on Day 1 C_{max} and AUC), reflective of dose-dependent anti-FVIII antibody formation neutralising activity of normal FVIII function. Anti-FVIII antibody formation was shown to peak at Day 35 at the 500 IU/kg dose level, with no sex difference. Similar findings were seen in animals dosed with pdFVIII but with lower antibody titres and no bruising, suggesting that pdFVIII was less immunogenic than simoctocog alfa in monkeys. Anti-FVIII antibody levels and FVIII levels recovered to some extent by the end of the 2 week recovery period. It is noted that animal models are not always reliable predictors of the immunogenicity of therapeutic proteins in humans.

- Genotoxicity and carcinogenicity studies were not conducted on simoctocog alfa, which is acceptable for a biological product. No reproductive toxicity data were provided, which is acceptable due to the chemical nature of simoctocog alfa. No effects on the reproductive organs were seen in histopathology assessment of reproductive organs in the 4 week repeat dose toxicity study in male and female monkeys. Studies in juvenile animals have not been provided but this omission is not unexpected because of the extensive clinical experience with rFVIII products.
- Local tolerance associated with IV injection was tested in rabbits. The perivenous injection of simoctocog alfa was well tolerated.
- In vitro tests using the EpiScreen™ assay with T cells from a panel of human donors indicated that simoctocog alfa is more immunogenic than the human plasma derived FVIII. The immunogenicity of simoctocog alfa was reduced by vWF to levels similar to the responses observed for human plasma derived FVIII. Overall, the in vitro results suggest a low risk of immunogenicity in humans.
- There are no nonclinical objections to the registration of Nuwiq for the proposed clinical use.
- The evaluator also recommended amendments to the draft Product Information but these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

The following rationale for the submission to register simoctocog alfa was provided by the sponsor 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 [11, 12]. 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

11Tuddenham EGD, Kannicht C, Agerkvist I, Sandberg H, Knaub S, Zozulya N. From human to humans - Introducing the first recombinant human FVIII product produced from a human cell line. Thromb Haemost Suppl 2010; 103: 4-14.
12Coppola A, Di Capua M, Di Minno MND, Di Palo M, Marrone E, Ieranò P, et al. Treatment of hemophilia: a review of current advances and ongoing issues. J Blood Med 2010; 1: 183-195.

normal) as mild (>5% to <40%), moderate (1% to 5%) or severe (<1%).[13]

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, 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.

Guidance

There is a European Medicines Agency (EMA) clinical guideline relevant to the application that has been adopted by the Therapeutic Goods Administration (TGA): *Note for guidance on the clinical investigation of recombinant FVIII and IX products (CPMP/BPWG/1561/99)*. However, this document has been superseded in the EU by the *Guideline on the clinical investigation of recombinant and human plasma-derived FVIII products (EMEA/CHMP/BPWP/144533/2009)*, which came into effect in the EU on 1 February 2012. The updated EU guideline had not yet been adopted by the TGA at the time of preparing this Clinical Evaluation Report (CER).[14]

The recent updated guideline relating to FVIII products is more stringent than the previous guideline as it specifically requires that the pre-marketing data include children (that is, 50 previously treated patients (PTPs) children aged 0 to 12 years for 50 exposure days (EDs), including PKs in 12 aged 6 to 12 years and 12 aged < 6 years), whereas the previous guideline specified that data in children were to be submitted after the market authorisation (that is, 20 PTPs aged < 6 years for 50 EDs or 6 months). In addition, the updated guideline has specific requirements relating to the submission of postmarketing authorisation data in previously untreated patients (PUPs), with suitable studies being initiated prior to market authorisation. In contrast, the previous guideline did not specifically require studies to be undertaken in PUPs but simply specified that treatment in PUPs be documented.

Contents of the clinical dossier

The submission included a comprehensive data package supporting approval of simoctocog alfa for the treatment of severe haemophilia A in previously treated adults and

[13]White GC, Rosendaal F, Aledort LM, Lusher JM, Rothschild C, Ingerslev J, et al. Definitions in hemophilia. Recommendations of the scientific subcommittee on FVIII and factor IX of the scientific and standardization committee of the International Society on Thrombosis and Haemostasis. Thromb Haemost 2001; 85: 560.
[14] The forementioned guideline was adopted by the TGA on 1 June 2014, during the evaluation process for this application.

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 PUPs with severe haemophilia A.

The clinical information provided in the dossier was as follows:

- Five clinical studies including GENA-01, -03, -08, -09 and -04; one of the five studies included data in children aged 2 to 12 years (GENA-03).
  - GENA-01, GENA-08 and GENA-03 were multinational (predominantly Western countries), pivotal studies. GENA-09, and its extension study GENA-04 were supportive studies conducted at a single centre in Russia that enrolled patients with severely affected joints and high historical bleeding rates.
  - PK data from two pivotal studies (GENA-01, GENA-03) and one supportive study (GENA-09); IVR data from the three pivotal studies (GENA-01, GENA-08, GENA-03) and the two supportive studies (GENA-09, GENA-04).
  - Efficacy and safety data from the three pivotal studies (GENA-01, GENA-08, GENA-03) and the two supportive studies (GENA-09, GENA-04).
- Literature references

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 to 5 years; 30 aged 6 to 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.

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).

Pharmacokinetics

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 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 (IVR, $t_{1/2}$), AUC and CL) are the most important (surrogate) endpoints for efficacy of a new FVIII product.[15]

The primary PK data were derived from 3 multinational, multicentre studies, including GENA-01 and GENA-08 in adults and GENA-03 in children aged 2 to 12 years. The supportive PK data were provided by two studies in adults, GENA-09 (a single-centre study undertaken in Russia that enrolled adult patients with severely affected joints and

[15] Lee M, Morfini M, Schulman S, and Ingerslev J. The Design and Analysis of Pharmacokinetic Studies of Coagulation Factors (Subcommittee on FVIII and Factor IX of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis). 21-Mar-2001.

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 five clinical studies included efficacy and safety data. Consequently, data from these five studies have been evaluated in the *Pharmacokinetics, Efficacy* and *Safety Sections* of the *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 full-length rFVIII concentrate BHK. In addition, GENA-01 included a formal bioequivalence analysis comparing simoctocog alfa with a full-length rFVIII BHK.

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 TGA adopted EU[16], 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 4.

Table 4: Overview of studies providing PK 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 2–12 years (26 for PK)	22 PTPs 18–62 years	18 PTPs who completed GENA-09
PK investigation (including IVR)	At baseline (full-length rFVIII comparator) and 6 months (only simoctocog alfa)	–	At baseline (comparator: previous FVIII concentrate)†	At baseline (full-length rFVIII comparator) and 6 months (only simoctocog alfa)	–
IVR investigation only	At 3 months	At baseline, 3 and 6	At baseline†, 3‡ and 6‡	At 3 months	At 3 months, then 3 monthl

[16] Guideline on the clinical investigation of recombinant and human plasma-derived FVIII products (EMEA/CHMP/BPWP/144533/2009)

	GENA-01 *Pivotal*	GENA-08 *Pivotal*	GENA-03 *Pivotal*	GENA-09 *Supportive*	GENA-04 *Supportive*
		months	months		y until study end
Immunogenicity	Yes	Yes	Yes	Yes	Yes
Efficacy	Yes	Yes	Yes	Yes	Yes
Safety	Yes	Yes	Yes	Yes	Yes

‡ All patients. † Patients not participating in the PK phase of the study. FVIII = coagulation FVIII; IVR = in vivo recovery; PK = pharmacokinetic; PTP = previously treated patient.

Evaluator's conclusions on pharmacokinetics

The PKs of simoctocog alfa have been satisfactorily characterised in previously treated adults and children aged 2 to 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), GENA-03 (26 children aged 2 to 12 years), and GENA-01 (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 PUPs. There were no PK studies specifically in adolescents aged > 12 years to ≤ 18 years, or in patients aged ≥ 65 years.

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 Chromogenic (CHR) and One-stage (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 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' full-length rFVIII BHK, as measured by both the CHR and OS assays. In this study, simoctocog alfa and 'licensed' full-length rFVIII BHK were bioequivalent based on the 90% confidence interval (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 BHK observed with both assays (14.7 versus 16.1 hours [CHR assay]; 17.1 versus 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 mean residence time (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 to 12 years. In children aged 2 to 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 to 5 years age cohort compared with the 6 to 12 years age cohort (0.22 versus 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 to 5 years age cohort compared with the 6 to 12 years age cohort (9.49 versus 9.99 hours, respectively), while the mean CL was higher (5.40 versus 4.33 mL/min/kg, respectively).

In children aged 2 to 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 versus 0.39 h•IU/mL per IU/kg, respectively), while the mean $t_{1/2}$ was shorter (9.73 versus 14.73 hours, respectively) and the mean CL was higher (4.89 versus 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 the paper by Bjorkman et al[17], IVR was lower, weight-adjusted clearance

[17]Bjorkman S et al. Comparative pharmacokinetics of plasma and albumin-free recombinant FVIII in children and adults: the influence of blood sampling schedule on observed age-related differences and implications for dose tailoring. Journal of Thrombosis and Haemostasis 2010;8:730-736.

was higher and FVIII half-life was lower in children with severe haemophilia A (aged 1 to 6 years of age) than in older patients (aged 10 to 65 years).

The IVR was assessed in all studies and was generally consistent across the studies. In GENA-08 (CHR assay), the mean ± standard deviation (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 to 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 to 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.[17] However, the lower 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 are 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.

Pharmacodynamics

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

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.[18] 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 to 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 ≥ 2 spontaneous bleeds during one month.

In the three pivotal studies (GENA-01, GENA-08, GENA-03), the simoctocog alfa dose for treating bleeds depended on the severity of bleeding. For minor bleeds, the dose was 20 to 30 IU FVIII/kg every 12 to 24 hours until bleed resolution. For major bleeds the dose was 30 to 40 IU FVIII/kg, repeated every 12 to 24 hours until bleed resolution. For major to life

[18]Lee M, Morfini M, Schulman S, and Ingerslev J. The Design and Analysis of Pharmacokinetic Studies of Coagulation Factors (Subcommittee on FVIII and Factor IX of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis). 21-Mar-2001.

threatening bleeds the initial dose was 50 to 60 IU FVIII/kg with subsequent doses of 20 to 25 IU FVIII/kg every 8 to 12 hours until bleed 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 to 30 IU FVIII/kg within 3 hours prior to surgery to achieve peak target level of approximately 50 to 60%, repeated every 12 to 24 hours until healing is complete, with trough level to be maintained at approximately 30%. For major surgical procedures, the dose was 50 IU FVIII/kg within 3 hours prior to surgery to achieve a target peak level of approximately 100%, repeated if necessary after 6 to 12 hours initially and for ≥6 days until healing is complete, with trough level to be maintained at approximately 50%.

Efficacy

Studies providing 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 5.

Table 5: 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 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 Pivotal	Phase III, prospective, multinational, multicentre, open-label, single-arm. Start: 22/07/2010. End: 31/01/2012.	32 adult PTPs enrolled: all 32 in ITT and SAF populations;	Determine the efficacy of simoctocog alfa during prophylactic treatment, treatment of BEs and in surgical prophylaxis.	Calculate incremental recovery; Investigate immunogenicity; Assess safety.

Study	Design	Patients	Primary objectives	Secondary objectives
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 Supp o-rtive	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 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 efficacy and safety in surgical prophylaxis.
GENA-04 Phase IIIb Supp o-rtive	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.

Evaluator's conclusions on efficacy

The submitted data are considered to have satisfactorily established the efficacy of simoctocog alfa for routine prophylaxis against bleeds, treatment of breakthrough bleeds 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 EU (and TGA adopted) guideline.[19] Overall, this guideline is more stringent than the previous EU guidance[20]. 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 EU 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 authorisation 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 human immunodeficiency virus (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 Bethesda unit (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.

[19] Guideline on the Clinical Investigation of Recombinant and Human Plasma-Derived FVIII Products (EMEA/CHMP/BPWP/ 144533/2009)
[20] Note for Guidance on the Clinical Investigation of Recombinant FVIII and IX products (CPMP/BPWG/1561/99)

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 to 6 years; 30 aged from 6 to 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 6.

Table 6: Key baseline characteristics 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 Haem A (%)	63.6%	56.3%	40.7%	54.5%	N/A
FVIII inhibitors**	0%	0%	0%	0%	N/A

Data expressed as mean (range) unless otherwise indicated.
* All 18 patients in GENA-04 participated in GENA-09. ** FVIII inhibitors (< 0.6 BUs). FH of Haem A = Family history of haemophilia A. N/A=not applicable

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 and two supportive studies with data is summarised below in Table 7.

Table 7: Summary of prophylactic treatment in pivotal studies.

	GENA-08 (n=32)	GENA-03 (n=59)	GENA-09 (n=22)	GENA-04 (n=18) *
Administered Dose	30-40 IU/kg every other day	30-40 IU/kg every other day or 3x/week	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 7 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 bleeding rate. The sponsor comments that this is a more stringent criterion than subjective criteria based on an individual investigator's assessment of the patient. In all four studies, a substantial majority of patients achieved excellent efficacy ratings (bleed< 0.75) for all bleeds and for spontaneous bleeds. The efficacy ratings for the three clinical studies with data for **all bleeds** at the end of the study are summarised below in Table 8.

Table 8: Efficacy of prophylactic treatment for All Bleeds.

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 9.

Table 9: Efficacy of prophylactic treatment for Spontaneous Bleeds*.

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 response to the questions arising from the first round evaluation of the submission. The

sponsor's responses to the Clinical questions and the evaluator's comments on the sponsor's responses are detailed in the Extract from the CER, Attachment 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 10.

Table 10: 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% versus 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 bleeds 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 11. 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 bleeds with available efficacy assessments being rated as excellent or good. Across all studies, efficacy was higher for minor than for moderate to major bleeds and nearly all treatments for minor bleeds across the five studies were rated as excellent or good. The percentage of children with moderate to major bleeds 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 11: Efficacy assessment for treatment of BEs with available data according to severity of the BE (any, minor, moderate to major).

	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	34.1%	28.6%	11.1%	31.9%	45.9%
Moderate	5.5%	-	15.7%	38.3%	8.1%
None	-	-	1.9%	-	
Minor BE	416	14	61	17	20
Excellent	75.0%	85.7%	86.9%	58.8%	70.0%
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

	GENA-01	GENA-08	GENA-03	GENA-09	GENA-04
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 bleeds 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 12 below). However, the sponsor states that taking into consideration that almost 50% of the bleeds 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 bleeds 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 5 studies was administered to a child (88 IU/kg).

Table 12: 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 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).*	FVIII peak levels 60-80%; dose 30-40 IU/kg every 12-24 h until BE resolution.	FVIII peak levels 40-60%; dose 15-30 IU/kg every 12-24 hr until BE resolution.
Major to life-	FVIII required levels 60-100%; dose 30-50	FVIII peak levels 100-	FVIII peak levels 100-120%; initial

Severity BE	Proposed Dose - based on PI	GENA-01, -08, -03, -04	GENA-09
threatening	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).*	120%; initial dose 50-60 IU/kg and subsequently 20-25 IU/kg every 8-12 h until BE resolution.	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 Summary of Product Characteristics (SmPC). (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 13. The data show that the IVR was notably lower in children (GENA-03) than in adults (GENA-01, GENA-08).

Table 13: 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
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-	26 -	CH	53.1 ±	1.83 ±	52.2	1.70 ±	51.6 ±	1.77 ±

n			IVR Start		IVR 3 months		IVR 6 months	
03	55 [3]	R	1.5	0.41 [4]	± 4.3	0.40	3.1	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 response to the questions arising from the first round evaluation of the submission. The sponsor's responses to the Clinical questions and the evaluator's comments on the sponsor's responses are detailed in the Extract from the CER, Attachment 2.

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 (total knee replacement (TKR) in GENA-04). Blood transfusions/fresh frozen plasma (FFP) were administered on 3 occasions to 2 patients in GENA-04 undergoing major surgery (1 total hip replacement (THR) and 1 revision in 1 patient; 1 TKR 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 von Willebrand disease (vWD).

The overall efficacy of simoctocog alfa for surgical procedures was evaluated intra-operatively and postoperatively, 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 the 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 14. 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 response to the questions arising from the first round evaluation of the submission. The sponsor's responses to the Clinical questions and the evaluator's comments on the sponsor's responses are detailed in the Extract from the CER, Attachment 2.

Table 14: 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%.

Safety

Studies providing 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.

Patient 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 and 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 15.

Table 15: Study drug exposure data; Safety populations.

Parameter	GENA-01 (n = 22)	GENA-08 (n = 32)	GENA-03 (n= 59)	GENA-09 (n = 22)	GENA-04 (n = 18)*
EDs per patient, n	53.3 18, 97	90.3 17, 105	96.1, 24, 152	97.7, 79, 132	226, 14, 299
Infusions per patient, n	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

Data are expressed as mean (range).* The 18 patients in GENA-04 had completed GENA-09. ED = exposure day; IU = international units.

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 (such as 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. For further details see Extract from the CER Attachment 2.

Comment: The relevant definitions for AEs were standard for clinical trials of the type included in the submission. All AEs were treatment-emergent. No time interval for collection of AEs could be identified.

Postmarketing data

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

Evaluator's 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 to 5 years, 30 aged 6 to 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.[21, 22]

The pooled safety data from the 5 clinical studies have been reviewed. In addition, the safety data in children aged 2 to 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 bleeds 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 (≥ 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

[21] Jovanovic BD and Levy PS. A look at the rule of three. The American Statistician 1997;51(2):137-139.
[22] Jacobson RM et al. Adverse events and vaccinations - the lack of power and predictability of infrequent events in pre-licensure study. Vaccine 2001; 19: 2428-2433.

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/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 System Organ Class (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 Hepatitis B virus (HBV) or Hepatitis C virus (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 'White'. There were no safety data in female patients. There were no safety data in PUPs with severe haemophilia A.

First round benefit-risk assessment

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 to 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 on 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.

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 to 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 to 5 years compared with the sub-group of children with aged 6 to 12 years with respect to any BEs, spontaneous BEs and traumatic BEs.

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%.

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

46.2% versus 30.3%, and none for 0% versus 6.1%.

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.

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 approximately 2 per 1000 patient-years.[23]

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

[23] Gouw SC, van den Berg HM: The Multifactorial Etiology of Inhibitor Development in Hemophilia: Genetics and Environment. Seminars in Thrombosis and Hemostasis 2009;35:723-734.

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 Independent Data Monitoring Committee (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 respiratory tract infection (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 Hepatitis B virus (HBV) or Hepatitis C virus (HCV) infection.

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.

First round recommendation regarding authorisation

It is recommended that simoctocog alfa (Nuwiq) be approved for:

> *Treatment and prophylaxis of bleeding (also during and after surgery) in previously treated patients with haemophilia A (congenital FVIII 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 PUPs 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 the second quarter of 2015 (GENA-99).

Clinical questions

Pharmacokinetics

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

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?

Safety

5. How long after the last dose of simoctocog alfa were AE 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 AEs)?
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 pruritus 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 the standardised medical dictionary for regulatory activities (MedDRA) queries (SMQ) search criteria for 'hypersensitivity', 'anaphylactic reactions' or 'allergic conditions' (high level group term (HLGT))?

Second round evaluation of clinical data submitted in response to questions

The sponsor's responses to the Clinical questions and the evaluator's comments on the sponsor's responses are detailed in the Extract from the CER, Attachment 2.

Second round benefit-risk assessment

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 evaluation.

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 evaluation.

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.

Second round recommendation regarding authorisation

It is recommended that simoctocog alfa (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 FVIII 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.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted an EU Risk Management Plan (EU-RMP), version 3, dated 8 August 2013 and an Australian Specific Annex (ASA), version 1, dated 12 August 2013 and EU-RMP, version 6.0, dated 16 May 2014 and ASA, version 3.0, dated 19 May 2014 which were reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 16.

Table 16. Sponsor's summary of ongoing safety concerns

Summary of safety concerns	
Important identified	None

Summary of safety concerns	
risks	
Important potential risks	Inhibitor development (antibodies against rFVIII) General tolerability (hypersensitivity and allergic reactions)
Important missing information	Safety in PUPs Use in pregnant or breast-feeding women

PUP = previously untreated patient; rFVIII = recombinant coagulation factor VIII.

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities for all ongoing safety concerns. In addition, one clinical study to investigate the immunogenicity in PUPs is ongoing, and a second clinical study to investigate the immunogenicity and long-term tolerability in PTPs is planned.

Risk minimisation activities

The sponsor proposes routine risk-minimisation activities for all ongoing safety concerns.

Reconciliation of issues outlined in the RMP report

Table 17 summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.

Table 17: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
1. Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated section 31 request and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	No safety considerations have been raised by the nonclinical evaluators. The responses to the safety considerations raised by the clinical evaluators have been evaluated. No impact for the RMP could be identified.	The response has been noted.
2. Amendments to the table of ongoing safety concerns.	2.1) 'Safety in patients with mild or moderate	2.1.) The addition of this ongoing safety concern to the table of

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
Notwithstanding the evaluation of the non-clinical and clinical aspects of the safety specifications (SS), the table of ongoing safety concerns is considered incomplete. Recommendations for changes are as follows. 2.1) Patients with mild and moderate haemophilia were not included in the clinical development program. Consequently, it is recommended that this patient group be included in the table of ongoing safety concerns as missing information. 2.2) Patients with severe renal and hepatic impairment were excluded from clinical development program. Consequently, it is recommended that this patient group be included in the table of ongoing safety concerns as missing information. 2.3) Only a very small number of patients (n=7) in the clinical development program were not Caucasian. Since the risk of development of antibodies is higher in the non-Caucasian patient population, it is recommended that 'Safety in patients with different ethnic origins' be included in the table of ongoing safety concerns as missing information. 2.4) Only one patient in Study GENA-08 was aged older than 65 years. Consequently, it is recommended that patients ≥65 years be included in the table of ongoing safety concerns as missing information. 2.5) Paediatric patients ≤2 years were excluded from the clinical development program and therefore, it is recommended	haemophilia A' has been included as missing information in the appropriate Sections of the RMP. 2.2) 'Safety in patients with renal or hepatic impairment' has been included as missing information in the appropriate Sections of the RMP. 2.3) 'Safety in patients with different ethnic origins' has been included as missing information in the appropriate Sections of the RMP. 2.4) 'Safety in elderly patients' has been included as missing information in the appropriate Sections of the RMP. 2.5) 'Children < 2 years' has already been included as missing information in the Risk Management Plan in response to the evaluation of the RMP by the European Medicines Agency (EMA). 2.6) The number of HIV positive patients or patients	ongoing safety concerns is considered acceptable. However, it is recommended to the Delegate that the wording used to address this ongoing safety concern in the PI be revised. 2.2.) The addition of this ongoing safety concern to the table of ongoing safety concerns is considered acceptable. However, it is recommended to the Delegate that the wording used to address this ongoing safety concern in the PI be revised. 2.3.) The addition of this ongoing safety concern to the table of ongoing safety concerns is considered acceptable. However, it is recommended to the Delegate that the wording used to address this ongoing safety concern in the PI be revised. 2.4.) The addition of this ongoing safety concern to the table of ongoing safety concerns is considered acceptable. Pending the Delegate's approval, the wording used in the PI to address this safety concern is considered acceptable. 2.5.) The addition of this ongoing safety concern to the table of ongoing safety

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
that this patient group be included in the table of ongoing safety concerns as missing information. 2.6) It appears that the sponsor does not specify the number of HIV positive patients or patients with other infections (including Hepatitis) in the RMP. It is recommended that the sponsor provides this information, and if only a small number of patients with these conditions were enrolled, then these patient groups should be included in the table of ongoing safety concerns as missing information. 2.7) Since this product will be administered by patients in a home treatment setting, it is recommended that 'Medication errors in the home treatment setting' be included as missing information in the table of ongoing safety concerns. 2.8) The risk for antibody development is increased in patients with high risk gene mutations and therefore, it is recommended that the sponsor adds 'Safety and tolerability in patients with high risk gene mutations' as missing information in the table of ongoing safety concerns.	with other infections enrolled in the clinical trial programme with Simoctocog alfa was included in Section SIV.3.9 of the RMP. Out of 135 patients, 48 patients were suffering from (an) infection(s) at study entry. Thereof, 8 patients were positive for HIV and 44 patients were positive for Hepatitis C. Some of the patients suffered from more than one infection. A detailed overview of the patients with infections in the clinical trial programme is presented in the RMP. No cases of FVIII inhibitors were observed in any of these patients. 'Safety in patients with HIV or other infections' has been included as missing information in the appropriate Sections of the RMP. 2.7) 'Medication error including safety in home therapy setting' has already been included as a potential risk in the Risk Management Plan in response to the evaluation of	concerns is considered acceptable. Pending the delegate's approval, the wording used in the PI to address this safety concern is considered acceptable. 2.6.) The addition of this ongoing safety concern to the table of ongoing safety concerns is considered acceptable. However, it is recommended to the Delegate that the wording used to address this ongoing safety concern in the PI be revised.* 2.7.) The addition of this ongoing safety concern to the table of ongoing safety concerns is considered acceptable. Pending the Delegate's approval, the wording used in the PI to address this safety concern is considered acceptable. 2.8.) The addition of this ongoing safety concern to the table of ongoing safety concerns is considered acceptable. However, it is recommended to the Delegate that the wording used to address this ongoing safety concern in the PI be revised.* * The sponsor has proposed to use the same generic wording to address all these safety concerns in the

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	the RMP by EMA. 2.8) 'Safety in patients with high risk gene mutations' has been included as missing information in the appropriate Sections of the RMP.	PI and CMI. This is considered not acceptable as it does not inform the health care professional and the patient about the absence of clinical data which could inform these ongoing safety concerns. It is recommended that the sponsor amends the PI and CMI to provide more precise information/recommendations.
3. It is recommended that the pharmacovigilance section of the ASA be amended to include reference to the TGA document 'Australian requirements and recommendations for pharmacovigilance responsibilities of sponsors of medicines', Version 1.1, December 2012.	Section 2 'Pharmacovigilance Practice' of the ASA has been amended to include reference to the TGA document 'Australian requirements and recommendations for pharmacovigilance responsibilities of sponsors of medicines', Version 1.2, August 2013.	This is considered acceptable.
4. The sponsor should amend the ASA to include reference to study GENA-13. If this study has been finalised, then the sponsor should update the EU-RMP to reflect this.	Reference to study GENA-13 has been included in Sections 2.2 and 2.3 of the ASA. This study is still ongoing.	This is considered acceptable.
5. The sponsor should provide an attachment to the ASA setting out all the forthcoming studies and the anticipated dates for their submission in Australia.	An overview of the forthcoming studies and the anticipated dates for submission of the study reports in Australia has been included in Sections 2.2 and 2.3 of the ASA.	This is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
6. It is recommended that the sponsor implements follow-up forms to collect data linked to inhibitor development and hypersensitivity reactions. These forms should be provided for review prior to approval.	Follow-up forms for inhibitor development and hypersensitivity reactions have already been prepared and included in Annex 7 of the RMP in response to the evaluation of the RMP by EMA. Additionally, according to the requirements received from the EMA, a follow-up questionnaire on suspected thromboembolic events has also been included in the RMP.	This is considered acceptable.
7. The sponsor should provide a table summarising the safety specification, pharmacovigilance plan and planned risk minimisation measures in Australian context in the ASA. Wording pertaining to important safety concerns in the proposed Australian PI and CMI should be included in the table.	Tables including the safety specification (Section 1) and the planned risk minimisation measures (Section 3) in the Australian context have been included in the ASA. Wording pertaining to safety concerns in the proposed Australian PI and CMI have also been included. The pharmacovigilance plan for Australia does not differ from the actions described in the EU-RMP. Section 2.3 of the ASA includes a table showing the safety	This is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	concerns that will be addressed by all ongoing and planned studies as well as the date of submission of the study reports in Australia.	
8. It is recommended to the Delegate to draw the attention of the nonclinical evaluator to assess whether 'Transmission for infectious reagents' should be added to the table of ongoing safety concerns as missing information.	No safety concerns were raised by the nonclinical evaluator.	The response has been noted.
9. Amendments to the CMI/PI were recommended but are beyond the scope of this AusPAR.	The CMI has been updated according to the recommendations. A tracked and clean copy of the CMI is provided.	This is considered acceptable.

ASA = Australian Specific Annex; CMI = Consumer Medicine Information; EMA = European Medicines Agency; HIV = human immunodeficiency virus; OPR = Office of Product Review; PI = Product Information; RMP = risk management plan.

Summary of recommendations

It is considered that the sponsor's response to the TGA S31 Request has not adequately addressed all of the issues identified in the RMP evaluation report (please refer to outstanding issues below).

Outstanding issues

Issues in relation to the RMP

It is recommended to the Delegate, that the sponsor amends the PI and Consumer Medicine Information (CMI), to provide more precise information about missing information in the PI and CMI.

***Advice from the** Advisory Committee on the Safety of Medicines (ACSOM)*

ACSOM advice was not sought for this submission.

Key changes to the updated RMP

In their response to the TGA's requests for further information the sponsor provided an updated RMP (version 6.0, dated 16 May 2014) and ASA, version 3.0, dated 19 May 2014). Key changes from the version evaluated in the first round are the addition of various missing information as requested by the RMP evaluator.

OPR evaluator's comments

The addition of the missing information in the table of ongoing safety concerns is considered acceptable. However, the risk-minimisation activities proposed for some of the missing information is not considered acceptable.

Suggested wording for conditions of registration

RMP

Implement EU-RMP, version 6.0, dated 16 May 2014 and ASA, version 3.0, dated 19 May 2014 and any future updates as agreed with the TGA as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There were no outstanding quality issues identified.

Batch Release Conditions were proposed for inclusion as specific conditions of registration.

Nonclinical

The nonclinical evaluation raised no objections to registration.

Clinical

Overview of data[24]

There were five clinical studies: GENA-01, -03, -04, -08 and -09. No study provided evidence for use in (a) previously untreated patients; and (b) patients <2 years of age. GENA-03 studied previously treated children (n=29 ages 2 to 5; n=30 aged 6 to 12).

Pharmacokinetics (PK)

Primary PK data were derived from GENA-01 and GENA -08 in adults, and GENA -03 in children.

GENA-01 generated PK data in 22 PTPs 12 to 65 years of age (median age 40 years; only 2 patients <18 years) with severe haemophilia A (HmA).

- In the first part of the study, comparison was made with full-length rFVIII BHK, using a cross-over design. Blood samples were taken at baseline and 11 more time-points over 48 hrs. Suitable PK endpoints were used. FVIII: C / time curves were superimposable for simoctocog alfa and full-length rFVIII BHK; minor differences in half-life and mean residence time across products were deemed by the evaluator to be clinically insignificant.
- In the second part of the study, PK for simoctocog alfa was assessed at 6 months in 21 patients. Minor differences were seen relative to PK at study start, with a decline in

[24] PTP = previously treated patient; PUP = previously untreated patient

exposure of approximately 5-10% apparent across various endpoints. An exploratory analysis excluding results from 6 patients at 1 Bulgarian study centre found less of a difference between time-points.

- Mean in vivo recovery (IVR) over time was in the 2.0 to 2.5% per IU/kg range, being closer to 2.5% with the chromogenic assay and 2.0% with the one stage assay.
- The one stage assay tended to deliver lower estimates of plasma FVIII than the chromogenic assay. The sponsor notes this has been observed with other B-domain deleted products.

GENA-03 studied PK in 59 PTPs 2-12 years of age with severe HmA.

- In the first part of the study (n=13 ages 2-5 years; n=13 ages 6-12 years), comparison was made with previously used FVIII (previous FVIII in cycle 1 then simoctocog alfa in cycle 2). Blood samples were taken at baseline and 6 more time points over 48 hours. FVIII: C/time curves were superimposable for simoctocog alfa and previous FVIII and PK parameters were similar, once dose-normalised. Time to C_{max} (T_{max}) was lower for simoctocog alfa than for previous FVIII. Most previous FVIII was plasma-derived (in 20/26), and PK results for previous FVIII varied according to whether recombinant or plasma-derived FVIII had been used; simoctocog alfa PK more closely resembled PK after pdFVIII, perhaps because only 6 subjects used rhFVIII so more variability may have been introduced because of the small sample.
- Results were analysed in the 2 to 5 year subgroup and the 6 to 12 year subgroup. There was a signal of a modest increase in dose-normalised exposure with simoctocog alfa relative to previous FVIII, in these younger subjects; but in the 6 to 12 year group the opposite trend emerged, suggesting variability due to sample size may have influenced outcomes.
- In the second part of the study, a further 32 patients were added and followed for at least 6 months and 50 exposure days, for safety / efficacy outcomes. In vivo recovery was also studied, at the start of Phase II, at 3 months and at 6 months. IVR ranged from 1.6 to 1.8% per IU/kg, by the chromogenic assay (1.3 to 1.6% per IU/kg by the one stage assay).

GENA-08 generated PK data in 32 PTPs 18-75 years of age (mean age 37 years) with severe HmA. In vivo recovery was assessed as a secondary endpoint (n=32 at visit 1; n=31 at 3 months; n=30 at 6 months); there was no other PK assessment. At Month 3 and at Month 6, IVR was 90 to 94% that of IVR at visit 1 but the clinical evaluator considered this of limited clinical significance.

GENA-09 was a PK study conducted at a single centre in Russia, in 22 PTPs with severe HmA (mean age 24.5 years; range 18 to 62), with evidence of inadequate prior treatment of HmA. Part I was a randomised cross-over with full-length rFVIII BHK; Part II was an uncontrolled assessment of prophylaxis. In Part I, after dose-normalisation, systemic exposure was lower for simoctocog alfa than for full-length rFVIII BHK. The explanation given by the sponsor, copied into the CER (Attachment 2), is plausible. At the 6 month time point, PK results for simoctocog alfa were broadly similar to those at Visit 1. IVR was assessed at Visit 1, 3 months and 6 months. At the later time-points, IVR using the OS assay was lower than at Visit 1, although the evaluator considered differences clinically unremarkable. In the follow-up study GENA-04 IVR was consistent to at least 15 months.

Differences in PK between children and adults are noted in the CER; differences observed were consistent with previously observed differences in PK of FVIII products between adults and children.

Efficacy

Studies GENA-01, GENA-08 and GENA-03 were considered pivotal.

GENA-01

GENA-01 enrolled 22 PTPs (≥150 EDs) 12 to 65 years of age with severe HmA (FVIII:C ≤1%). Reference has been made to Part I (PK) above. In Part II (efficacy), patients completing Part I were followed for 6 months or until 50 EDs were reached, whichever came last. Patients with prior inhibitor activity were excluded.

Part II assessed efficacy of on-demand and surgical use of simoctocog alfa. It did not study prophylaxis (but short-term prophylaxis to prevent recurrent bleeding after a bleeding event [BE] was allowed). Dosages used to treat BEs were standard. Frequency and treatment of bleeds is described in the CER (Attachment 2). Efficacy was summarised in the CER as follows:

Table 18: 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).

Increasing severity of bleeds was matched by a shift towards lower efficacy, although there were few 'major to life-threatening' BEs (the three such BEs are described on CER Attachment 2). Some 96.8% of BEs were treated successfully with 1 to 2 infusions. Of individual infusions (n=1041), 90.4% were considered as having excellent or good efficacy, 8.5% as having moderate efficacy and 0.9% (n=9) as having no efficacy. The infusions with no efficacy were in two individual patients.

Two patients underwent surgery (1 major, 1 minor). There was no indication of poor haemostatic control in either case.

GENA-08

GENA-08 enrolled 32 PTPs (≥150 EDs) 18 to 75 years of age with severe HmA (FVIII: C ≤1%). The study assessed efficacy in prophylaxis, on-demand (that is, breakthrough BEs while on prophylaxis) and surgical settings. Treatment was to 6 months / 50+ EDs. Prophylaxis involved 30-40 IU/kg every other day; two dose escalations of 5 IU/kg were allowed in case of an inadequate response (2+ spontaneous BEs in a month).

No BEs were reported in 16/32 subjects. 11/32 subjects reported 1 BE in the study; 5/32 subjects reported 5-8 BEs. Excluding BEs during surgical prophylaxis and BEs prior to prophylactic treatment, the mean monthly bleeding rate per patient was 0.188 (median 0.074); the Delegate's calculation of the annualised bleeding rate is therefore 2.3 (mean) and 0.9 (median). Comparison with pre-study outcomes is described on CER and copied below:

Table 19: 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.

While dose increased, so did efficacy. A patient was identified with a prior low BE rate, where the BE frequency was 10 fold higher on-study (4 of the 5 BEs were traumatic). Efficacy of simoctocog alfa in treating breakthrough BEs was acceptable, with a median of 1 infusion required (3 subject required 6- 12 infusions).

There were five surgical procedures in 5 patients where ≥1 dose of simoctocog alfa was given; 4 procedures were major. Efficacy in one joint arthroscopy ('major') was rated as moderate – requiring 25 infusions – after intra-operative assessment of good efficacy; but otherwise efficacy was rated as excellent.

GENA-03

GENA-03 enrolled 29 patients aged 2 to 5 years and 30 patients aged 6 to 12 years of age who were previously treated (≥50 EDs) for severe HmA (FVIII:C <1%). PK aspects (Phase I of the study) were described earlier. Phase II assessed prophylaxis and use of simoctocog alfa on-demand in the treatment of breakthrough bleeding events. Dosing was every other day or three times weekly, for at least 6 months and at least 50 EDs. Two dose escalations of 5 IU/kg were allowed in case of 2+ BEs in a month.

A patient discontinued after failure of simoctocog alfa to prevent/treat a spontaneous ankle joint bleed. Eleven patients had dose escalations.

Overall efficacy of prophylaxis is summarised in the CER (Attachment 2). Of 59 subjects, outcomes were excellent in 49, good in 5, moderate in 3 and poor in 2. Four of five moderate to poor outcomes were in the 30 patients aged 6 to 12 years. Based on the monthly rate of bleeding events, mean (median) annualised bleeding rates were 2.6 (0) for 2 to 5 year olds and 5.5 (3.6) for 6-12 year olds. Comparison with historical outcomes is presented in the CER; results were comparable.

Overall efficacy of treatment of BEs is described in the CER; 81% of bleeds were treated with 1 to 2 infusions but 9/108 BEs required 5 to 22 infusions. Efficacy was rated only as moderate in 46.2% of moderate to major bleeds in 2 to 5 year olds and 30.3% of moderate to major bleeds in 6 to 12 year olds; 2/33 moderate to major bleeds in 6 to 12 year olds had poor efficacy.

Efficacy in surgery is described in the CER. There were 6 major procedures where prophylactic simoctocog alfa was used, one in a patient diagnosed with vWD who was withdrawn from study (simoctocog alfa was not efficacious and the patient needed

pdFVIIIa product containing both vWF and FVIII – for a moderate to major bleed following the procedure). Five out of six procedures were port implants or replacements. One patient undergoing port implantation needed 20 infusions over 7 days but there were no associated BEs or complications reported. Efficacy was assessed as excellent in all 5 procedures where an assessment was made.

Other studies

Studies GENA-09 (single Russian centre study of every other day prophylaxis in adult PTPs with severe HmA) and GENA-04 (extension of GENA-09) were considered supportive.

The 22 patients in GENA-09 had severe joint damage. Mean annualised bleeding rate (calculated from monthly rates) was 4.1. For spontaneous bleeds, efficacy of treatment was often excellent or good but in 38% of cases was rated only moderate. Compared with historical outcomes, dose of FVIII rose while bleeding rates fell substantially. There were no major surgical procedures.

In GENA-04, with a mean 226 EDs per patient there was evidence of ongoing efficacy of prophylaxis. Mean number of infusions used to stop breakthrough bleeding was 2. For some moderate to major bleeds, efficacy was rated as moderate (17.6% of BEs) or none (17.6%). There were 3 major surgeries, requiring 23-35 infusions over 15-20 EDs, but blood loss was lower than predicted and overall efficacy was rated good in 3/3 cases.

Safety

Some 135 patients received simoctocog alfa; exposure is summarised in the CER. Commoner AEs included nasopharyngitis (8.1%), pyrexia (7.4%), headache (7.4%) and rhinitis (5.2%). Cases of chills, rash and pruritus, and a case of allergic oedema of the left hand, were thought by the sponsor unlikely to be allergic reactions to simoctocog alfa, and the clinical evaluator accepted this.

There were no hypersensitivity reactions to simoctocog alfa and no thromboembolic events identified. No FVIII inhibitors were detected (although 4 patients developed anti-FVIII antibodies described as non-inhibitory; indicates 3/4 had these prior to using simoctocog alfa and the other one patient had low levels that did not affect efficacy). In 0/4 patients was there a sign of functional impairment of FVIII.

In GENA-08, one patient died after 76 EDs from an epileptic seizure on Day 202. This was deemed unrelated to study treatment. The patient had been on long-term therapy with oxycarbazepin for epilepsy, but died after status epilepticus.

Clinical evaluator's recommendation (if applicable)

The clinical evaluator 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 <u>severe</u> haemophilia A (congenital FVIII 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.

Risk management plan

No objections to registration were raised. A proposed condition of registration was:

> Implement EU-RMP, version 6.0, dated 16 May 2014 and ASA, version 3.0, dated 19 May 2014 and any future updates as agreed with the TGA as a condition of registration.

Risk-benefit analysis

Delegate's considerations

Dosing

The dose regimens recommended in the proposed PI are based on the European Core Summary of Product Characteristics (SmPC) for FVIII products[25], and do not align perfectly with dosing protocols used in GENA studies. The Delegate agrees with the clinical evaluator that the sponsor's approach as indicated in the latest PI is acceptable.

Inhibitors

Absence of inhibitors in the clinical trial population of previously treated patients with no history of inhibitors does not indicate absence of risk of inhibitor development in previously untreated patients. Inhibitors in children mostly develop within 20 EDs or by 20 months of age.[26] Throughout life, a bimodal distribution of inhibitor onset has been described[27]; but the trial program did not study many older patients.

Furthermore, too few patient-years were accumulated in this population at low risk for inhibitor development (that is, non-elderly PTPs) to determine whether the risk of inhibitor development with simoctocog alfa is in line with other FVIII agents. Absence of inhibitors is reassuring to only a limited extent.

There were some individual episodes equating to treatment failure or poor efficacy; it would have been reassuring to have inhibitor assay results around the time of these events of inefficacy, or subsequently, to rule out inhibitor development as a cause. The sponsor is invited to discuss in the Pre-Advisory Committee on Prescription Medicines (ACPM) response if inhibitors were measured around the time of events of poor or no efficacy, or subsequently, for example the two patients in GENA-01 discussed in the CER who had in total 9 infusions without efficacy; the patient in GENA-03 whose bleeding was not managed by simoctocog alfa and who discontinued as a result; others in GENA-03 rated as having poor prophylactic efficacy. The sponsor is also invited to comment on the trend across PK studies for mean IVR to decline at 6 months compared with baseline; was this mean decline due to outliers with significant declines, and, if so, could this be linked to untested / unrecognised inhibitor development?

Surgery

Across studies, there were 13 'major' procedures in 12 patients. Efficacy was excellent in 9/13 (69.2%), good for 3/13 (23.1%) and moderate for 1/13 (7.6%).

Indication

The currently proposed indication from the sponsor is:

> *Treatment and prophylaxis of bleeding (also during and after surgery) in previously treated paediatric (≥ 2 years) and adult patients with haemophilia A (congenital FVIII deficiency).*

The clinical evaluator suggests that the indication be restricted to those subjects with severe HmA. This approach reflects study inclusion criteria. The Delegate considers the currently proposed indication acceptable. Recent precedent has been to approve

[25]http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128995.pdf

[26] Gouw SC, van der Bom JG, Ljung R, Escuriola C, Cid AR, Claeyssens-Donadel S, et al. FVIII products and inhibitor development in severe hemophilia A. N Engl J Med 2013; 368: 231-239.

[27] Hay CR, Palmer B, Chalmers E, Liesner R, Maclean R, Rangarajan S, et al. Incidence of factor VIII inhibitors throughout life in severe hemophilia A in the United Kingdom. Blood 2011; 117: 6367-6370

treatment without reference to disease severity, which allows clinicians more flexibility in use of the agent.

A question for the ACPM is whether there should be a statement that Nuwiq does not contain von Willebrand Factor and is not indicated in von Willebrand's disease (see Product background for some currently registered agents and their approved indications.)

The ACPM is invited to comment on any aspect of the PI/CMI that could be improved.

Summary of issue/s

Previously untreated patients were not studied. Patients under 2 years of age were not studied. Only those with severe haemophilia A were studied.

Dosing recommendations in PI are different to dose regimens used in the trial program.

Proposed action

The Delegate had no reason to say, at this time, that the application for Nuwiq should not be approved for registration but the advice of the Committee is requested. See below.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Should the indication limit use to subjects with severe Haemophilia A?
2. Should the indication include a statement that the product does not contain vWF and is not indicated to treat von Willebrand's Disease?
3. Are dosing recommendations acceptable given their departure from dosing in pivotal studies?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Issue 1: Inhibitors

The Sponsor was invited to comment on whether inhibitor development be ruled out as a cause of individual episodes equating to treatment failure or poor efficacy. The sponsor was also invited to comment on the trend across PK studies for mean IVR to decline at 6 months compared with baseline; was this mean decline due to outliers with significant declines, and, if so, could this be linked to untested / unrecognised inhibitor development?

Sponsor's comment:

Poor efficacy and inhibitor development

In 3 patients (9 infusions) in GENA-01 for which the efficacy rating for bleed treatment was 'none'. Inhibitor tests with plasma samples obtained around the time of the infusions with an efficacy rating as 'none' were negative (Table 17). Efficacy ratings for the next infusions for the subsequent bleeds were 'moderate' or 'good'. This suggests that the negative efficacy ratings were not related to the development of an inhibitor, but rather were incidental singular events.

Table 17: Individual patient results.

Patient	Efficacy rating as 'none' for individual infusions	Date and efficacy rating of next individual infusion for next bleed	Negative inhibitor results* around time infusions with efficacy rating of 'none'
1	24 January 2011 (2x) 27 January 2011	10 February 2011 *'Good'*	10 January 2011 7 April 2011
2	16 April 2011 (2x) 18 April 2011	20 April 2011 '*Moderate*'	18 February 2011 06 May 2011
3	23 May 2011 24 May 2011 25 May 2011	27 May 2011 *'Good'*	6 May 2011 19 September 2011

* All inhibitor results in all studies were negative.

In one patient (X) in GENA-03, treatment failure was documented on 13 May 2011. The last previous inhibitor test with the plasma sample obtained on 12 April 2011 was negative. Following withdrawal from the study, the patient switched back to his previous FVIII concentrate. Inhibitor testing is performed at this study centre regularly (at least twice per year) by the Bethesda assay (Nijmegen modification). A follow up with the investigator revealed that the patient had been tested six times (between 07 June 2011 and 28 January 2014) for the presence of inhibitors. Each time, the test was negative. This suggests that the failed therapy was not related to the development of an inhibitor.

Prophylactic efficacy was rated as 'poor' (monthly bleeding rate > 1.5). Patient X participated only for a relatively short time (71 days) in the study during which he experienced three bleeds and was withdrawn due to therapy failure. All inhibitor tests during the study and afterwards were negative (see above). Patient Y experienced 13 bleeds, 12 of which were traumatic, which pointed to an active lifestyle of this young boy (age 9 years). All inhibitor tests were negative. In summary, this suggests that the poor prophylactic efficacy was not related to the development of an inhibitor.

IVR decline and inhibitor development

The sponsor agrees with the expert's assessment that the IVR was generally consistent across studies and that it also was consistent over time within a study.

The trend toward a lower mean IVR over time may be perceived to have occurred in GENA-01; however, the decrease was not statistically significant and the decrease in the median values over time was not obvious: IVR (CHR assay) at study start was 2.46 (% per IU/kg), 2.49 after 3 months and 2.41 after 6 months.

Issue 2: Indication

The currently proposed indication from the sponsor is:

> *Treatment and prophylaxis of bleeding (also during and after surgery) in previously treated paediatric (≥ 2 years) and adult patients with haemophilia A (congenital factor VIII deficiency).*

The Clinical Evaluator suggests that the indication be restricted to those patients with severe haemophilia A (see Attachment 2). This approach reflects study inclusion criteria. I consider the currently proposed indication acceptable. Recent precedent has been to approve treatment without reference to disease severity, which allows clinicians more flexibility in use of the agent.

A question for the ACPM is whether there should be a statement that Nuwiq does not contain vWF and is not indicated in vWD (see Attachment 2).

Recommended changes to the PI are at Attachment 3. The ACPM is invited to comment on any aspect of the PI/CMI that could be improved.

Sponsor's comment:

With reference to the restriction of the indication to 'severe haemophilia A', Octapharma would like to comment that the mechanism of action, that is, substitution of missing FVIII, is the same, regardless of whether severe, moderate or mild haemophilia A patients need substitution therapy. The Nuwiq studies were designed in accordance with the EMA guidelines which require that studies are performed in severe haemophilia A patients (otherwise it would be difficult to accumulate enough exposure days allowing a reasonable statement regarding long-term safety and efficacy). Therefore, Octapharma believes it is justified to keep the indication without limitation to severe haemophilia A, as also noted by the Delegate.

With reference to the question for the ACPM for including a statement that Nuwiq is not indicated for vWD, Octapharma agrees to include the following statement in the PI under 'Indications': '*Nuwiq does not contain von Willebrand factor and is thus not indicated to treat von Willebrand's disease.' The CMI has also been updated accordingly in the section 'What Nuwiq is used for' with the statement 'Nuwiq does not contain von Willebrand factor and is therefore not suitable to treat von Willebrand's disease*.'

The PI and CMI have been amended as per the recommendations; however, in circumstances where a recommended change has not been agreed to by Octapharma, a justification was provided. The details of these are beyond the scope of this AusPAR.

1. *The indication should be amended to include reference to severe haemophilia A.*

   As per the Delegate's recommendation in Attachment 3, the PI has not been amended to include a limitation to 'severe' haemophilia A. As also stated in our response to Issue 2 (page 2), Octapharma does not believe that a limitation to the indication is justified as the mechanism of action, i.e. substitution of missing FVIII, is the same, regardless of whether severe, moderate or mild haemophilia A patients need substitution therapy. The Nuwiq studies were also designed in accordance with the EMA guidelines which require that studies are performed in severe haemophilia A patients (otherwise it would be difficult to accumulate enough EDs allowing a reasonable statement regarding long-term safety and efficacy).

2. Outstanding issues – Issues in relation to the RMP:

It is recommended to the Delegate, that the sponsor amends the PI and CMI, to provide more precise information about missing information in the PI and CMI.

Sponsor's comment:

Missing information has been included in the PI or justification provided for not including the recommended information.

Details of these discussions are beyond the scope of this AusPAR.

3. Key changes to the updated RMP:

In their response to the TGA requests the sponsor provided an updated RMP (version 6.0, dated 16 May 2014) and ASA, version 3.0, dated 19 May 2014.). Key changes from the version evaluated at Round 1 are the addition of various missing information as requested by the RMP evaluator.

OPR Evaluator's comments: The addition of the missing information in the table of ongoing safety concerns is considered acceptable. However, the risk minimisation activities proposed for some of the missing information is considered not acceptable.

Sponsor's comment:

An updated ASA to the RMP, with the requested information, has been prepared.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register a new biological entity.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered Nuwiq powder for injection containing 250, 500, 1000 and 2000 IU per vial of simoctocog alfa to have an overall positive benefit–risk profile for the amended indication**;**

> *Simoctocog alfa is indicated in adults and children (≥ 2 years) with haemophilia A (congenital FVIII deficiency) for:*
>
> - Control and prevention of bleeding episodes.
> - Routine prophylaxis to prevent or reduce the frequency of bleeding episodes.
> - Perioperative management (surgical prophylaxis).
>
> *Simoctocog alfa does not contain von Willebrand factor, and therefore is not indicated in patients with von Willebrand's disease.*

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically advised on the inclusion of the following:

- Negotiation of Product Information and Consumer Medicines Information to the satisfaction of the TGA.
- Submission to the TGA, as soon as available, any post market study reports such as those recommended in the relevant EMA guideline.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- A statement in the *Clinical Trials* section of the PI to reflect that doses for prophylaxis in clinical trials were 30 to 40 IU/kg.
- A clarification of the cumbersome procedure for giving separate vials where individual doses are not combined by being drawn up in single syringe but by using multiple syringes. The ACPM advised that the proposed 2.5 ml volume is unwieldy for use in

children under 10 years who routinely have an infusaport administration (10 mL is needed).

- The ACPM advised the use of the term "Prolonged" rather than "Profuse" as a general descriptor for bleeding, as profuse bleeding only occurs in rare circumstances.
- A list of excipients should be included in case of hypersensitivity reactions.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. Should the indication limit use to subjects with severe Haemophilia A?

The ACPM advised that, while the relevant guideline recommended trials only in patients with severe Haemophilia A the guideline also considered extrapolation to less severe forms to be reasonable. The ACPM agreed with this view.

3. Should the indication include a statement that the product does not contain vWF and is not indicated to treat von Willebrand's Disease?

The ACPM agreed such a statement was appropriate.

4. Are dosing recommendations acceptable given their departure from dosing in pivotal studies?

The ACPM noted that the sponsor had agreed to minor changes in dosage tables as suggested by the clinical evaluator and the delegate agreed these were acceptable. The ACPM was of the view that the approach as per the most recent PI was acceptable.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Nuwiq powder and solvent for injection containing simoctocog alfa 250IU, 500IU, 1000IU and 2000IU for IV administration indicated for:

> *Treatment and prophylaxis of bleeding (also during and after surgery) in previously treated paediatric (≥ 2 years) and adult patients with haemophilia A (congenital FVIII deficiency).*
>
> *Nuwiq does not contain von Willebrand factor and is thus not indicated to treat von Willebrand's disease.*

Specific conditions of registration applying to these goods

1. The Nuwiq EU-RMP Risk Management Plan (RMP), version 6.0, dated 16 May 2014 and ASA, version 3.0, dated 19 May 2014 and any future updates as agreed with the TGA will be implemented in Australia.
2. It is a condition of registration that, as a minimum, the first five independent batches of

   -Nuwiq Human cell line recombinant human FVIII (Human-cl rhFVIII), 2000IU, powder and solvent for solution for injection

   - Nuwiq Human cell line recombinant human FVIII (Human-cl rhFVIII), 1000IU, powder and solvent for solution for injection

- Nuwiq Human cell line recombinant human FVIII (Human-cl rhFVIII), 250IU, powder and solvent for solution for injection

- Nuwiq Human cell line recombinant human FVIII (Human-cl rhFVIII), 500IU, powder and solvent for solution for injection

imported into/manufactured in Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA's Office of Laboratories and Scientific Services (OLSS).

Attachment 1. Product Information

The Product Information approved for main Nuwiq at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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