Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Efmoroctocog alfa (rhu)[1]

Proprietary Product Name: Eloctate

Sponsor: Biogen Idec Australia Pty Ltd

Date of CER:
2 October 2013

TGA Health Safety Regulation

[1] At the time of submission and registration the non-proprietary name for Eloctate was efrlaloctocog alfa. The name was changed on 20 February 2015 to efmoroctocog alfa to harmonise with the approved International Nonproprietary Name for this product. This document has been edited by replacing efralocotocog alfa with efmoroctocog alfa.

About the Therapeutic Goods Administration (TGA)

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

About the Extract from the Clinical Evaluation Report

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

Contents

List of abbreviations

Abbreviation	Meaning
ADA	anti-rFVIIIFc binding antibody
ADA	Adverse event
ALT	alanine aminotransferase
ASA	acetylsalicylic acid
AST	aspartate aminotransferase
AUC	area under the curve
BNP	brain natriuretic peptide
BU	Bethesda unit
BUN	blood urea nitrogen
CI	confidence interval
CSR	clinical study report
ED	exposure day
EMA	European medicines agency
EPD	electronic patient diary
FAS	Full Analysis Set
FVIII	coagulation factor VIII
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HJHS	Haemophilia Joint Health Score
IgG	immunoglobulin G
IgG1	immunoglobulin G1
ISTH	the International Society on Thrombosis and Haemostasis

Abbreviation	Meaning
IU	international unit
IV	intravenous
IXRS	Interactive Voice/Web Response System
LFT	liver function test
LTE	long-term extension (study)
MRT	mean residence time
NSAID	non-steroidal anti-inflammatory drug
PK	pharmacokinetic
PKAS	Pharmacokinetic Analysis Set
PTP	previously treated patient
PUP	previously untreated patient
QoL	quality of life
rFVIII	recombinant coagulation factor VIII
rFVIIIFc	recombinant coagulation factor VIIIFc fusion protein
SAE	serious adverse event
SOC	system organ class
TGA	Therapeutic Goods Administration
ULN	upper limit of normal
URTI	upper respiratory tract infection
VWF	von Willebrand factor

1. Introduction

This is a Category 1 submission to register a new chemical entity (Type A): Eloctate powder for injection. The proposed indication is:

> *Eloctate is a long-acting antihaemophilic factor (recombinant) indicated in adults and children (≥12 years) with haemophilia A (congenital factor VIII deficiency) for control of bleeding episodes, routine prophylaxis to prevent or reduce the frequency of bleeding episodes, and perioperative management (surgical prophylaxis).*

2. Clinical rationale

Haemophilia is an inherited, X-linked bleeding disorder. In Australia there are approximately 2,600 people with haemophilia and nearly all are male. Haemophilia A is the most common form and is due to the deficiency of factor VIII. Reduced blood coagulation results in bleeding which is most commonly internal, usually into the joints or muscles. Over time, recurrent bleeds can cause permanent damage such as arthritis, chronic pain and joint damage requiring surgery. Plasma derived coagulation factor concentrates were effective but were associated with a high rate of blood-borne viruses such as hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV). Effective recombinant factor VIII products have been developed subsequently although their use is limited by the development of inhibitor (anti-rFVIIIFc binding antibody (ADA)) in up to 30% of patients. Inhibitors develop most commonly within 100 exposure days in previously untreated patients (PUPs) but may also develop in previously treated patients (PTPs). The next generation of recombinant products will be long-acting with the aim of reducing the frequency of the intravenous (IV) injections required for long-term prophylaxis in patients with severe disease.

Eloctate is a replacement therapy to increase plasma factor VIII levels as a temporary correction of the bleeding tendency in haemophilia A. The coagulation factor VIII (FVIII) portion of Eloctate is a glycoprotein similar to endogenous FVIII found in human plasma. When injected, it binds to von Willebrand factor in the circulation and acts as a replacement for the FVIII deficiency. The other portion of Eloctate is the Fc fragment of human immunoglobulin G1 (IgG1) which binds to the neonatal Fc receptor which is expressed throughout adult life. This receptor protects immunoglobulins from lysosomal degradation and acts to prolong their plasma half-life. The design of Eloctate enables replacement of all the functions of FVIII with an extended half-life compared with the naturally occurring factor.

2.1. Guidance

A pre-submission meeting with the TGA was held. The sponsors were requested to justify the use of a single pivotal study, and to justify the lack of randomisation in the clinical trial program in the proposed submission. However, the TGA provisionally accepted the sponsors' justification for the lack of an active comparator control in the pivotal study. Such a non-inferiority study would not be feasible because of the large patient numbers required in the orphan haemophilia population.

The TGA has adopted the European medicines agency (EMA) guideline on recombinant coagulation factor VIII (rFVIII) products (1999[2]) but the latest guideline (2009[3]) has not yet been adopted. The TGA has encouraged the sponsor to comply with the earlier guideline but has sought the opinion of the clinical evaluator before considering potential discrepancies further.

2.2. Orphan drug designation

The Delegate of the Secretary designated recombinant human coagulation factor VIII Fe fusion protein as an orphan drug *for the control and prevention (including routine prophylaxis) of bleeding episodes in adults and children with haemophilia A* on 23 February 2013.

2 CPMP/BPWG/1561/99. Note for guidance on the clinical investigation of recombinant factor VIII and IX products

3 EMA/CHMP/BPWP/144533/2009. Guideline on the clinical investigation of recombinant and human plasma-derived factor VII products.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

Module 5

- One Phase I/IIa clinical pharmacology study (998HA101), a completed pharmacokinetic (PK) study in previously treated patients.
- One population pharmacokinetic analysis (CPP-12-026-BIIB031, derived from clinical studies 998HA101 and 997HA301).
- One pivotal Phase III efficacy/safety study A-LONG (997HA301), an open-label, uncontrolled, 3 arm study in previously treated adult patients.
- One interim progress report of the supportive efficacy/safety study (8HA01EXT), an ongoing study in previously treated adult patients who have completed 997HA301, and paediatric patients who have completed 8HA02PED.

Module 1

- Application letter, application form, draft Australian product information (PI) and consumer medicine information (CMI).

Module 2

- Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety, Summary of Clinical Pharmacology, Summary of Biopharmaceutic and Analyitical Methodsand literature references.

3.2. Paediatric data

The submission included one efficacy/safety study (8HA02PED), a progress report of an ongoing study in previously treated paediatric patients < 12 years with completed patients continuing into 8HA01EXT.

Data from these studies will form the basis of a future submission for use in children.

3.3. Good clinical practice

All studies were conducted in compliance with the principles of the ICH guidelines on Good Clinical Practice (GCP) and the eithical principles outlined in the Declaration of Helsinki.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

Pharmacokinetic study 998HA101and the population pharmacokinetic report CPP12-026-BIIB031 were provided in the dossier. None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

4.2.1. Pharmacokinetics in healthy subjects

No studies performed.

4.2.2. Pharmacokinetics in the target population

PK study 998-HA-101 and the population PK analysis CPP-12-026-BIIB031 were provided in the dossier.

4.2.3. Pharmacokinetics in other special populations

4.2.3.1. Pharmacokinetics in subjects with impaired hepatic function

No studies have been performed.

4.2.3.2. Pharmacokinetics in subjects with impaired renal function

No studies have been performed.

4.2.3.3. Pharmacokinetics according to age

No studies have been performed.

4.2.3.4. Pharmacokinetics related to genetic factors

No studies have been performed.

4.2.3.5. Pharmacokinetics in other special populations

No studies have been performed.

4.2.4. Pharmacokinetic interactions

4.2.4.1. Pharmacokinetic interactions demonstrated in human studies

No studies have been performed.

4.2.4.2. Clinical implications of in vitro findings

There are no clinical implications of in vitro studies.

4.3. Evaluator's overall conclusions on pharmacokinetics

The activity-time profiles of recombinant coagulation factor VIII Fc fusion protein (rFVIIIFc) have been evaluated and compared with Advate in a Phase I/IIa PK study in 16 patients with haemophilia A. The study used FVIII activity as a surrogate endpoint as recommended by the EMA and the International Society on Thrombosis and Haemostasis (ISTH) to estimate area under the curve (AUC), half-life, mean residence time (MRT) and clearance. rFVIIIFc had a superior PK profile compared with Advate with approximate increases in half-life and MRT of 53% for the 25 international unit (IU)/kg dose and 76% for the 65 IU/kg dose. The prolongation of activity was due to a 36% reduction in the clearance of rFVIIIFc compared to Advate. The primary PK profile was based on the one-stage clotting assay and confirmed by similar results using the chromogenic assay. The compartmental and non-compartmental analyses were complemented by the population PK analysis which confirmed the long-term stability of the PK parameters. The population PK models adequately described the activity data in the PK and Phase III studies. The major covariate for rFVIIIFc activity was clearance and there was no clinically meaningful influence related to body weight, haematocrit or age.

The PK and the pivotal studies were well conducted and complied with TGA and EMA guidelines. The combined data have been used to develop useful dosing recommendations for clinicians.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

None submitted.

6. Dosage selection for the pivotal study

Doses of 25 IU/kg and 65 IU/kg were well tolerated in the Phase I/IIa study 998HA101. Based on the PK data it was estimated that 88% of patients would sustain FVIII trough levels > 1% 3 days after a 25 IU/kg dose and that 83% of patients would sustain trough levels > 1% 4 days after a 50 IU/kg dose. Based on these assumptions, the starting dose for Arm 1 of the pivotal study was a twice-weekly regimen with 25 IU/kg on the first day followed by 50 IU/kg on the fourth day. Data from 998HA101 were also used to generate dose adjustment algorithms for individualised prophylaxis regimens.

7. Clinical efficacy

7.1. For control of bleeding episodes, routine prophylaxis to prevent the frequency of bleeding episodes, and perioperative management (surgical prophylaxis)

7.1.1. Pivotal efficacy studies

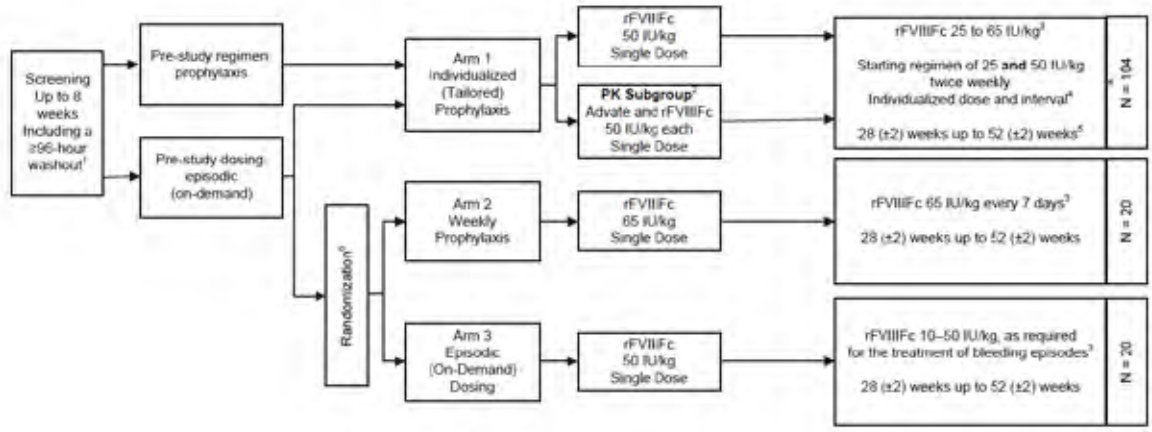
7.1.1.1. Study 997HA301 (A-LONG)

7.1.1.1.1. Study design, objectives, locations and dates

This was an open label, multicentre evaluation of the safety, efficacy and PK of rFVIIIFc in the prevention and treatment of bleeding in previously treated patients with severe haemophilia A. The design complies with EMA guidelines.

The objectives of the study were to compare the efficacy and safety of rFVIIIFc given in various treatment regimens as prophylaxis and on-demand during surgical treatment. The other main objective was to compare the PK profiles of rFVIIIFc and Advate, the current standard treatment for haemophilia A. The study population was males aged ≥ 12 years with severe haemophilia A defined as < 1 IU/dL endogenous FVIII and who had at least 150 days of previous exposure to any FVIII product. The study schema is shown below in Figure 1.

Figure 1: Study 997HA301 (A-LONG) schema.



- Arm 1: Individualised (Tailored) Prophylaxis
  - Initial twice weekly dosing with 25 IU/kg of rFVIIIFc on Day 1 and 50 IU/kg on Day 4, followed by individualised dose and interval modification within the range of 25 to 65 IU/kg every 3 to 5 days to maintain a trough level of 1% to 3% (or higher, as clinically indicated) rFVIIIFc.
  - Approximately 104 patients
- Arm 2: Weekly prophylaxis
  - 65 IU/kg rFVIIIFc every 7 days
  - Approximately 20 patients
- Arm 3: Episodic (On-Demand) Dosing
  - Initial single dose of 50 IU/kg rFVIIIFc followed by 10 to 50 IU/kg rFVIIIFc, as required to treat a bleeding episode
  - Approximately 20 patients

An additional 2 subgroups were defined:

- Arm 1: Sequential PK subgroup in 16 patients for estimation of the PK profiles and terminal half-lives of rFVIIIFc and Advate.
- Arms 1, 2 and 3, Perioperative Management (Surgery) Subgroup: patients from any arm who required major surgery. A minimum of 10 major surgeries in at least 5 patients were planned. Patients who required minor surgery remained in their assigned arms.

The total study duration was 75 weeks for the sequential PK subgroup and up to 67 weeks for all other patients, depending upon the assigned treatment arm. The screening period was up to 8 weeks with a FVIII wash-out period of 96 hours for adults and 72 hours for adolescents aged ≥ 12 to 17 years. Randomisation into Arms 1 and 2 occurred on Day 0 when the first rFVIIIFc treatment was given. All study patients were expected to receive between 28 (± 2) and 52 (± 2) weeks of an rFVIIIFc treatment regimen. Patients who completed the study were offered entry into a long-term extension (LTE) study under a separate protocol 8HA01EXT.

7.1.1.1.2. Inclusion and exclusion criteria

The main inclusion criteria were males aged ≥ 12 years with severe haemophilia A; at least 150 days previous treatment with any FVIII product; no measurable inhibitor activity in 2 consecutive samples; documented history of bleeding events and/or treatment with FVIII

during the previous 12 weeks; platelet count ≥ 100,000 cells/µL; CD4 count > 200 mm^3 in known HIV patients; viral load < 400 copies/mL if known HIV positive.

The main exclusion criteria were: history of or currently detectable inhibitor; other coagulation disorder in addition to haemophilia A; history of hypersensitivity or anaphylaxis to any FVIII or immunoglobulin; current or likely use of acetylsalicylic acid (ASA) or non-steroidal anti-inflammatory drugs (NSAIDs); concurrent treatment with immunosuppressive drugs with certain exceptions for HCV and HIV; major surgery within the previous 8 weeks; abnormal renal function (serum creatinine > 2.0 mg/dL); serum alanine aminotransferase (ALT)>5x upper limit of normal (ULN); and bilirubin > 3xULN.

7.1.1.1.3. Study treatments

The rFVIIIFc was supplied as a kit containing lyophilised drug, a diluent, a vial adaptor and an infusion set. The lyophilised drug was provided in four strengths in 10 mL clear glass vials containing 250, 500, 1000 or 2000 IU of rFVIIIFc. Commercially available Advate was used for the PK comparator sub-study.

7.1.1.1.4. Efficacy variables and outcomes

The main efficacy variables were:

- Bleeding events (spontaneous and traumatic) as recorded by patients in the electronic patient diary (EPD)
- Patients' self-assessment of the response to rFVIIIFc treatment on a four point scale (Excellent, Good, Moderate and No Response)
- Investigators' assessment of the response to treatment on a four point scale (Excellent, Effective, Partially Effective and Ineffective)
- Investigator/Surgeons' four point assessment of response to treatment following surgery (Excellent, Good, Fair, and Poor/None)
- quality of life (QoL) questionnaire data
- PK data

The primary efficacy outcomes were:

- The annualised number of bleeding episodes (spontaneous and traumatic) Arm 1 versus Arm 3.
- Primary PK assessments of FVIII activity.

Other efficacy outcomes included:

- Annualised number of bleeding episodes Arm 2 versus Arm 3
- Total annualised rFVIIIFc consumption per patient
- Investigators' assessment of patients' response to treatment
- Annualised number of spontaneous bleeding episodes
- Time from last injection of rFVIIIFc to a bleeding episode
- Investigator/Surgeons' assessment of patients' response to surgery

7.1.1.1.5. Randomisation and blinding methods

After confirmation of eligibility, patients were randomised using interactive voice/web response system (IXRS). Patients who were on a prophylaxis regimen prior to study entry were entered into Arm 1 (individualised prophylaxis); patients who were on an episodic regimen had the option to enter either Arm 1, or to be randomised into either Arm 2 (weekly prophylaxis) or

Arm 3 (episodic, on-demand dosing). Randomisation into Arms 2 or 3 was stratified based on the number of bleeding episodes reported by the patient during the 12 months prior to screening (12 to 20; 21 to 50; or > 50 episodes per year).

7.1.1.1.6. Analysis populations

- All-Enrolled Analysis Set defined as patients who enrolled by IXRS
- Full Analysis Set (FAS) defined as patients who received at least one dose of rFVIIIFc
- Safety Analysis Set defined as patients who received at least one dose of rFVIIIFc or Advate
- Pharmacokinetic Analysis Set (PKAS) defined as patients who completed evaluable sampling time-points sufficient to permit determination

Of the 165 patients in the All-enrolled set, 99.4% were included in the FAS; 100% were included in the Safety Set and 93.9% were included in the PKAS. Total treatment duration for rFVIIIFc is shown in Table 1.

Table 1: Study 997HA301. Duration of dosing with rFVIIIFc

Duration of dosing with rFVIIIFc
Safety analysis set

	Arm 1 (N=118)	Arm 2 (N=24)	Arm 3 (N=23)	Total (N=165)
Cumulative number of weeks on rFVIIIFc (a)				
At least 13 weeks	116 (99.1%)	20 (83.3%)	23 (100.0%)	159 (97.0%)
At least 26 weeks	112 (95.7%)	16 (66.7%)	18 (78.3%)	146 (89.0%)
At least 39 weeks	23 (19.7%)	0	0	23 (14.0%)	
At least 52 weeks	6 (5.1%)	0	0	6 (3.7%)
Total weeks on rFVIIIFc				
n	117	24	23	164
Mean (SD)	34.2 (8.19)	24.4 (9.73)	28.1 (3.80)	31.9 (8.78)
Median	32.1	28.0	28.9	30.5
Min, Max	9, 54	<1, 38	15, 32	<1, 54

NOTE 1: Percentages are based on the number of subjects who received rFVIIIFc in each treatment arm or overall. Subject 581-002 (Arm 1) received only Advate.
2: Time on rFVIIIFc refers to the length of time from the first rFVIIIFc PK dose through the last day of the efficacy period.
(a) A subject can appear in more than one category.

7.1.1.1.7. Sample size

Because of limited numbers in the haemophilia orphan population, the sample size of approximately 144 patients in three treatment arms was based on clinical rather than statistical considerations, taking into account the EMA Guidance 2009, which recommends a minimum of 100 patients.

7.1.1.1.8. Statistical methods

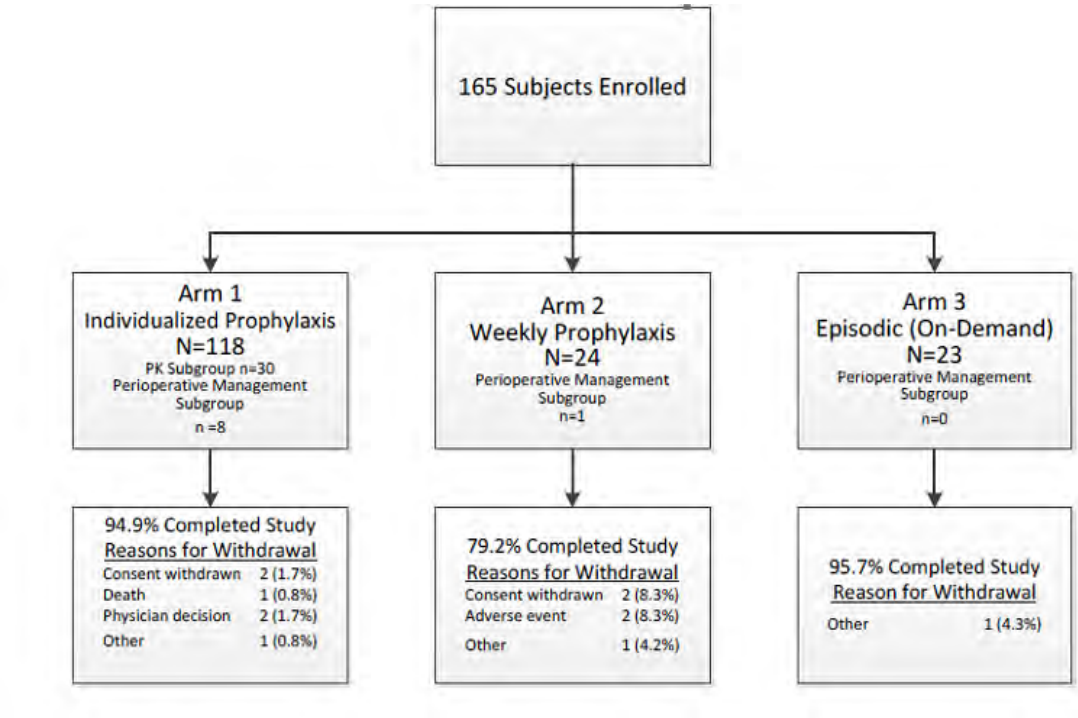
The primary endpoint was the annualised number of bleeding episodes (spontaneous and traumatic) during the efficacy period. All results were produced using Statistical Analysis System (SAS) Version 9.2. The comparison of annualised bleeding episodes between Arm 1 and Arm 3 was assessed using a negative binomial Poisson[4] regression model with the dependent variable 'total bleeding episodes' and the covariate as 'treatment arm'. The log of the efficacy period in years was fitted as an offset variable. Statistical significance was controlled at the 2-sided 0.05 level. Test results were tabulated by treatment with the bleeding rate ratios and their 95% confidence interval (CI). No adjustments for multiplicity were applied.

[4] The comparison was assessed by both negative binomial model and Poisson regression model. Since over dispersion is statistically significant the negative binomial regression model was used.

7.1.1.1.9. Participant flow

Patient flow is shown below in Figure 2. A total of 165 patients were enrolled and 153 completed the study (92.7%). In Arm 1, 118 patients were randomised[5] and 94.9% completed the study. In Arm 2, 24 patients were randomised and 79.2% completed. In Arm 3, 23 patients were randomised and 95.7% completed. There was a low withdrawal rate, the most common reason being withdrawal of consent. Two patients withdrew because of adverse events (AEs) and one patient died (of suicide).

Figure 2: Patient flow.



7.1.1.1.10. Major protocol violations/deviations

Major protocol deviations occurred in 67 patients (40.9%) 12 patients (7.3%) took excluded medication; 7 patients (4.3%) did not meet inclusion/exclusion criteria; 44 patients (26.8%) had informed consent issues; 9 patients (5.5%) had investigational product issues; and 9 patients (5.5%) had other major deviations. Deviations considered likely to affect the primary endpoint were provided.

Compliance with both prophylaxis regimens was high with 93.6% of patients compliant with dose and interval for at least 80% of their doses and 80% of their dosing intervals. For patients on a prior prophylaxis regimen, 87.4% received injections at least 3 times weekly. The majority of patients (146) received at least 26 weeks of treatment. A total of 111 patients had more than 50 days exposure, of whom 110 had a valid inhibitor test.

7.1.1.1.11. Baseline data

Demographics were representative of the general haemophilia A population and similar in all treatment arms. All patients were male with a median age of 30 years (range 12 to 65 years) and 13 patients in the ≥ 12 to 17 age group. The majority (91.5%) were aged between 18 and 64 years. Of the 165 enrolled patients, 64.8% were White, 26.1% were Asian and 6.1% were Black. The median weight was 71.6 kg (range 42.0 to 127.4 kg) and median BMI was 23.9 kg/m2 (range 15.3 to 37.4 kg/m2).

[5] There was no randomisation for Arm 1, and therefore it should state that 118 patients were enrolled.

Baseline disease characteristics are shown in Table 2. All patients had severe haemophilia and 153 patients had FVIII activity < 1% at screening or baseline. All patients had previous exposure to FVIII of at least 150 days. The median von Willebrand factor (VWF) antigen levels (which protect FVIII from proteolytic degradation) were similar in each treatment group. The proportion of patients with blood type O (who have lower FVIII levels than with other blood types) was approximately similar in each group. The number of bleeding episodes in the prior 12 months is shown in Table 3. The median number of bleeds in the individualised prophylaxis arm was 6.0. The median number of bleeds in the episodic treatment arms ranged from 24.0 to 29.5. Joint status measured by Haemophilia Joint Health Score (HJHS) was similar in all groups, consistent with patients with severe haemophilia. At baseline the median scores were 18.0 (Arm 1), 16.0 (Arm 2), 27.0 (Arm 3), and 20.0 (total group).

Table 2: Study 997HA301. Summary of haemophilia history.

Summary of hemophilia history
Safety analysis set

	Arm 1 (N=118)	Arm 2 (N=24)	Arm 3 (N=23)	Surgery subgroup (N=9)	Total (N=165)
Genotype (a)					
Intron 22 inversion	41/117 (35.0%)	7/ 21 (33.3%)	9/ 23 (39.1%)	2/ 9 (22.2%)	57/161 (35.4%)
Frameshift	24/117 (20.5%)	4/ 21 (19.0%)	6/ 23 (26.1%)	2/ 9 (22.2%)	34/161 (21.1%)
Missense	22/117 (18.8%)	4/ 21 (19.0%)	1/ 23 (4.3%)	3/ 9 (33.3%)	27/161 (16.8%)
Nonsense	19/117 (16.2%)	6/ 21 (28.6%)	1/ 23 (4.3%)	1/ 9 (11.1%)	26/161 (16.1%)
Splice site change	7/117 (6.0%)	0	4/ 23 (17.4%)	1/ 9 (11.1%)	11/161 (6.8%)
Intron 1 inversion	3/117 (2.6%)	0	1/ 23 (4.3%)	0	4/161 (2.5%)
Duplication	1/117 (0.9%)	0	0	0	1/161 (0.6%)
N/A	0	0	1/ 23 (4.3%)	0	1/161 (0.6%)
Von Willebrand factor (b)	118.0 (10, 327)	129.0 (48, 274)	131.0 (55, 380)	104.0 (10, 161)	118.0 (10, 380)
Blood type O (a)	46/118 (39.0%)	7/ 24 (29.2%)	10/ 23 (43.5%)	3/ 9 (33.3%)	63/165 (38.2%)
Est. bleeds prior 12 mths (b)	12.0 (0, 120)	29.5 (12, 59)	24.0 (12, 100)	17.0 (0, 120)	16.0 (0, 120)
Pre-study FVIII regimen (a)					
Prophylaxis	87/118 (73.7%)	0	0	4/ 9 (44.4%)	87/165 (52.7%)
On-demand	31/118 (26.3%)	24/ 24 (100.0%)	23/ 23 (100.0%)	5/ 9 (55.6%)	78/165 (47.3%)
>=1 target joints (a)	73/118 (61.9%)	22/ 24 (91.7%)	18/ 23 (78.3%)	5/ 9 (55.6%)	113/165 (68.5%)
Family history of inhibitor (a)	4/118 (3.4%)	1/ 24 (4.2%)	2/ 23 (8.7%)	0	7/165 (4.2%)
HIV positive (a)	25/118 (21.2%)	4/ 24 (16.7%)	7/ 23 (30.4%)	3/ 9 (33.3%)	36/165 (21.8%)
HCV positive (a)	55/118 (46.6%)	14/ 24 (58.3%)	13/ 23 (56.5%)	4/ 9 (44.4%)	82/165 (49.7%)

Table 3: Study 997HA301. Number of bleeding episodes in the prior 12 months.

Prestudy FVIII Regimen	Arm 1 Individualized Prophylaxis (N=118)		Arm 2 Weekly Prophylaxis (N=24)		Arm 3 Episodic Dosing (N=23)	
	n	Median	n	Median	n	Median
Prophylaxis	86	6.0	0	--	0	--
Episodic	31	27.0	24	29.5	23	24.0

Note: The number of bleeding episodes in the prior 12 months was unknown for one subject in Arm 1.

Consistent with the population of patients with severe haemophilia, 80% had joint disease and 35.8% had hepatitis. At baseline, 21.8% were HIV positive and 49.7% had HCV. Prior FVIII treatment regimens used prior to Day 1 are shown in Table 4. Of the 165 randomised patients, 52.7% were on a FVIII prophylaxis regimen and 73.7%[6] of patients enrolled in Arm 1. Of the 87 patients who were on a prophylaxis regimen prior to study entry, 1 (1.1%) reported a dosing frequency of one injection per week, 10 (11.5%) reported two injections per week, and 76 (87.4%) reported three or more injections per week. The most frequently used FVIII product before study entry was rFVIII (75.2%). The median doses typically used to treat a bleeding

[6] This percentage is the percentage of the subjects in Arm 1 who were on prophylaxis prior to the study. Per study design, all subjects who were on a prophylaxis regimen were enrolled in Arm 1.

episode were 25.0 IU/kg (range 3 to 68 for minor bleeds), 30.0 IU/kg (range 3 to 68 for moderate bleeds), and 50.0 IU/kg (range 3 to 100 for severe bleeds).

Table 4: Study 997HA301. Pre-study FVIII regimen; safety analysis set.

	Arm 1 - Tailored prophylaxis (N=118)	Arm 2 - Weekly dosing (N=24)	Arm 3 - On demand (N=23)	Surgery subgroup (N=9)	Total (N=165)
Pre-study FVIII regimen (a)					
Prophylaxis	87 (73.7%)	0	0	4 (44.4%)	87 (52.7%)
On-demand	31 (26.3%)	24 (100.0%)	23 (100.0%)	5 (55.6%)	78 (47.3%)
Time on pre-study FVIII regimen (b)					
> 12 months	98 (83.1%)	20 (83.3%)	20 (87.0%)	7 (77.8%)	138 (83.6%)
6 - 12 months	6 (5.1%)	1 (4.2%)	1 (4.3%)	1 (11.1%)	8 (4.8%)
< 6 months	14 (11.9%)	3 (12.5%)	2 (8.7%)	1 (11.1%)	19 (11.5%)

NOTE 1: Percentages are based on the number of subjects in each arm or overall.
2: Subjects in the surgery subgroup are also counted in the other arm in which they participated.
Each subject is counted once in the total column.
(a) Pre-study FVIII regimen is the most recent regimen the subject was receiving prior to the study.
(b) Calculated from start of pre-study FVIII date to screening date.

7.1.1.1.12. Results for the primary efficacy outcome

The principal outcomes were the annualised bleeding rate per patient and comparison between the prophylaxis and episodic regimens. The primary endpoint was the comparison between Arm 1 and Arm 3. The main secondary endpoint was the comparison between Arm 2 and Arm 3.

The annualised bleeding rate over the efficacy period is shown for Arms 1, 2, and 3, and compared between Arms 1 and 3 and Arms 2 and 3 in Table 5. The annualised bleeding rate estimated from the negative binomial model was 2.91 (95% CI: 2.30, 3.68) in Arm 1, 8.92 (95% CI: 5.48, 14.51) in Arm 2, and 37.25 (95% CI: 24.03, 57.74) in Arm 3. The bleeding rate ratios were 0.08 ($p < 0.001$) for Arm 1 versus Arm 3, and 0.24 ($p < 0.001$) for Arm 2 versus Arm 3, indicating significant reductions of 92% (Arm 1) and 76% (Arm 2) for prophylaxis or weekly prophylaxis compared with episodic treatment. No bleeding episodes were reported for 53 (45.3%) patients in Arm 1 and four (17.4%) patients in Arm 2. All patients in Arm 3 experienced bleeding episodes.

Table 5: Study 997HA301. Summary of bleeding episodes; full analysis set.

	Arm 1 - Tailored prophylaxis (N=117)	Arm 2 - Weekly dosing (N=24)	Arm 3 - On demand (N=23)	Total (N=164)
Total subject-years followed (a)	73.16	10.58	12.10	95.83
Total bleeding episodes per subject				
n	117	23	23	163
Mean (SD)	1.6 (2.54)	4.0 (7.00)	19.8 (11.74)	4.6 (8.29)
Median	1.0	1.0	18.0	2.0
25th, 75th percentile	0.0, 3.0	1.0, 4.0	11.0, 27.0	0.0, 4.0
Min, Max	0, 14	0, 30	5, 47	0, 47
0	53 (45.3%)	4 (17.4%)	0	57 (35.0%)
1	16 (13.7%)	8 (34.8%)	0	24 (14.7%)
2	16 (13.7%)	4 (17.4%)	0	20 (12.3%)
3	12 (10.3%)	0	0	12 (7.4%)
4	6 (5.1%)	4 (17.4%)	0	10 (6.1%)
5	5 (4.3%)	0	1 (4.3%)	6 (3.7%)
>5	9 (7.7%)	3 (13.0%)	22 (95.7%)	34 (20.9%)

A sensitivity analysis was performed which excluded 12 patients with major protocol deviations with potential to affect the primary endpoint. The results were similar to the primary analysis with median annualised bleeding rates of 1.60, 3.59 and 33.57 in Arms 1, 2, and 3, respectively (Table 6). A sensitivity analysis performed after adjustment for at least 80% compliance with study treatment also demonstrated similar results to the primary analysis.

Table 6: Study 997HA301. Annualised bleeding rates.

Annualized Bleeding Rate (Episodes/Year)	Arm 1 (N = 117) n (%)	Arm 2 (N = 24) n (%)	Arm 3 (N = 23) n (%)
0	53 (45.3%)	4 (17.4%)	0
>0-5	36 (30.8%)	11 (47.8%)	0
>5-10	21 (17.9%)	3 (13.0%)	1 (4.3%)
>10-20	7 (6.0%)	1 (4.3%)	2 (8.7%)
>20-30	0	2 (8.7%)	6 (26.1%)
>30-40	0	1 (4.3%)	7 (30.4%)
>40-50	0	0	2 (8.7%)
>50	0	1 (4.3%)	5 (21.7%)

Note: Efficacy endpoints were analyzed for 23 subjects in Arm 2; Subject 360-001 withdrew after the PK evaluations (no efficacy evaluations could be made).

A total of 13 patients aged 12 -17 years were included in the primary analysis. In the 11 adolescent patients randomised to Arm 1, the median annualised bleeding rate was 1.92 (range 0 – 7.1) compared with 1.44 (range 0 - 18.2) in the 105 patients in the 18 to 64 years age group.

7.1.1.1.13. Results for other efficacy outcomes

- Overall, 77.6% of rFVIIIFc injections were rated by patients as having an excellent or good response. Only 0.7% of injections were rated as having no response.
- A low annualised bleeding rate was observed for spontaneous, traumatic, and unknown site bleeding episodes in patients on a prophylaxis regimen (Table 7).

Table 7: Study 997HA301. Summary of annualised bleeding episodes by type of bleed. Full analysis set.

Type of bleed	Arm 1 - Tailored prophylaxis (N=117)	Arm 2 - Weekly dosing (N=24)	Arm 3 - On demand (N=23)	Total (N=164)
Spontaneous				
n	117	23	23	163
Mean (SD)	1.70 (2.971)	5.23 (9.023)	26.17 (17.812)	5.65 (11.468)
Median	0.00	1.93	20.24	1.07
25th, 75th percentile	0.00, 2.03	0.00, 4.78	12.21, 36.81	0.00, 5.17
Min, Max	0.0, 16.7	0.0, 32.8	1.7, 71.1	0.0, 71.1
Traumatic				
n	117	23	23	163
Mean (SD)	1.17 (1.951)	3.58 (6.697)	10.84 (13.046)	2.87 (6.566)
Median	0.00	1.69	9.25	0.00
25th, 75th percentile	0.00, 1.83	0.00, 3.27	1.74, 11.92	0.00, 3.17
Min, Max	0.0, 9.1	0.0, 25.1	0.0, 45.3	0.0, 45.3
Unknown				
n	117	23	23	163
Mean (SD)	0.04 (0.252)	0.00 (0.000)	0.22 (0.583)	0.06 (0.310)
Median	0.00	0.00	0.00	0.00
25th, 75th percentile	0.00, 0.00	0.00, 0.00	0.00, 0.00	0.00, 0.00
Min, Max	0.0, 1.6	0.0, 0.0	0.0, 1.7	0.0, 1.7

- The median interval between the last injection of rFVIIIFc administered to treat a bleeding episode and each new bleeding episode was longer for those patients on prophylaxis compared with episodic treatment. The median interval between the last injection of rFVIIIFc administered to treat a bleeding episode and a new bleeding episode was longer for patients treated with prophylaxis (19.83 for Arm 1 and 8.0 days for Arm 2) compared with patients treated episodically (6.55 days).
- Overall, 97.8% of bleeding episodes were controlled with ≤ 2 injections of rFVIIIFc with 87.3% controlled by one injection. Per bleeding episode, the median dose per injection required for resolution of bleeding was 27.35 IU/kg, and the median total dose required was 28.23 IU/kg.
- There was an improvement in QoL from baseline in prophylaxis patients who had switched from prior episodic therapy.
- Nine major surgeries were performed and haemostasis was rated by the investigators/surgeons as excellent or good in all cases. A total of 14 minor surgical procedures were performed in 12 patients and haemostasis was rated as excellent or good in all cases.
- The Investigators' Global Assessment for Patients' Response to rFVIIIFc was excellent or effective for 99.3% of the patients' visits.

7.1.2. Analyses performed across trials (pooled analyses and meta-analyses)

Only one efficacy study has been performed.

7.1.3. Evaluator's conclusions on clinical efficacy for control of bleeding episodes, routine prophylaxis to prevent or reduce the frequency of bleeding episodes, and perioperative management (surgical prophylaxis).

Because of the limited availability of haemophilia A patients, the latest EU Guideline EMA/CHMP/BPWP/144533/2009 (not yet adopted by the TGA) recommends the enrolment of at least 100 patients, using FVIII activity as a surrogate endpoint and without the need for a control group. The initial study should be conducted in PTPs aged ≥ 12 years with a study in PUPs conducted post-marketing. In the pivotal study, a total of 165 patients were randomised and all were PTPs. Patient numbers were adequate and 13 adolescent patients were included.

Despite the lack of a control group, the study clearly demonstrated that rFVIIIFc is effective in adults and adolescents with haemophilia A. In the pivotal Phase III study, there were 757 bleeding episodes of which 97.8% were controlled with ≤ 2 rFVIIIFc injections (87.3% with one injection) with a total median dose of 28 IU/kg. A total of 78.1% of patients evaluated the response to the first injection as excellent or good. The Investigators' global assessment of response was rated as excellent or effective for 99.3% of the patient visits. Prophylactic treatment was more effective than episodic treatment. In Arm 1 of the pivotal study (prophylaxis tailored to FVIII trough levels), 45.3% of patients had no bleeding episodes during the efficacy period with a 92% reduction ($p < 0.001$) in annualised bleeding rate compared with Arm 3 (the episodic treatment group). Single dose weekly prophylaxis was less effective than tailored prophylaxis but 14.5% of patients in Arm 2 had no bleeding episodes during the study. Nine major surgeries were performed in nine patients during the study. The response to rFVIIIFc was excellent in eight cases and good in one case after a single pre-operative dose to maintain haemostasis (median dose 51.4 IU/kg).

The study conduct was satisfactory and the efficacy results support the use of rFVIIIFc for control of bleeding episodes, routine prophylaxis and peri-operative management.

8. Clinical safety

8.1. Studies providing evaluable safety data

Study 997HA301 provided evaluable safety data. There were few AEs in the PK study 998HA101 with no serious adverse events (SAEs) or deaths. The study contributed less than 0.2% of the total rFVIIIFc exposure and these safety data are not assessed further.

· Pivotal efficacy studies.

In the pivotal efficacy study, the following safety data were collected:

– AEs, SAEs and deaths

– AEs of special interest, including inhibitor development, anaphylaxis, hypersensitivity events, serious thrombotic events, or suspected infectious agent transmission were reported to the Sponsor as SAEs irrespective of whether they met the criteria for SAEs.

– Laboratory tests were performed at a central laboratory.

· Pivotal studies that assessed safety as a primary outcome.

No studies have been performed.

· Dose-response and non-pivotal efficacy studies.

No studies have been performed.

· Other studies evaluable for safety only.

8.1.1. Study 8HA02PED

This is an open label, multicentre evaluation of the efficacy, safety and PK of rFVIIIFc for routine prophylaxis in paediatric previously treated patients with haemophilia A. The first patient was enrolled in August 2012 and the study is still ongoing. The cut-off point for this interim analysis was January 2013. The data have been used for evaluation of SAEs and AEs of special interest and no efficacy data have been analysed. No site information is included in the interim clinical study report (CSR).

Approximately 50 patients (25 patients < 6 years of age and 25 aged 6 to < 12 years) are planned to complete at least 26 weeks of treatment to obtain at least 50 exposure days per patient. At least 24 patients will be enrolled into the PK subgroup first. The remaining patients will proceed directly to twice weekly prophylaxis treatment after the PK results from the patient subgroup are available. Study visits will occur every five weeks and surgery will be allowed in the study. The study population will be paediatric PTPs < 12 years of age with severe haemophilia A defined as endogenous FVIII levels < 1 IU/dL and who have had at least 50 exposure days to FVIII products and no detectable inhibitor.

The primary objective of the study is to evaluate the safety of rFVIIIFc in paediatric PTPs with haemophilia A. The primary endpoint of the study is the frequency of inhibitor development. The secondary objectives are:

· To evaluate the efficacy of rFVIIIFc for prevention and treatment of bleeding episodes.

· To evaluate the PK of rFVIIIFc.

· To evaluate rFVIIIFc consumption for prevention and treatment of bleeding episodes.

· To evaluate the effect of rFVIIIFc based on patient-reported outcomes and health outcomes.

At the cut-off point, 33 patients have been enrolled into the study and 23 have received at least one dose of rFVIIIFc. Patient demographics were provided. Of the 33 patients, 33% were

< 6 years old and the remainder were aged in the range 6 to 12 years. The majority of patients were White (58%) and 21% were Black.

To date, no deaths have been reported. One treatment emergent SAE has been reported: a device-related infection considered unrelated to treatment.

8.1.2. Study 8HA01EXT

This is an extension study to the Phase III study 997HA301 and the paediatric study 8HA02PED. It is an open label, multicentre evaluation of the long-term safety and efficacy of rFVIIIFc for prophylaxis and episodic (on demand) treatment of bleeding episodes in previously treated patients (PTPs) with haemophilia A. The first patient was enrolled in December 2011 and the study is still ongoing. The cut-off date of this progress report is January 2013 and it was used to evaluate major surgery data, SAEs and AEs.

The primary objective of the study is to evaluate the long-term safety of rFVIIIFc. The secondary objective is to evaluate the efficacy of rFVIIIFc in the prevention and treatment of bleeding episodes. Patients will follow either an individualised prophylaxis regimen, weekly prophylaxis regimen, or episodic (on-demand dosing) based on the individual patient profiles and by the trough and peak (recovery) FVIII values noted in the previous study (either 997HA301 or 8HA2PED). The starting dose in 8HA01EXT will be based on the patient's PK profile obtained in the previous study. Patients are allowed to change treatments (for example, from prophylaxis to episodic dosing or the converse) during the study, based on investigator judgement. Patients who require surgery may be treated with rFVIIIFc in any way seemed fit by the investigator. Scheduled visits will occur every 6 months with unscheduled visits as required.

The primary endpoint is the frequency of inhibitor development. The secondary endpoints are:

- The number of annualised bleeding episodes (spontaneous and traumatic) per patient.
- The number of annualised spontaneous joint bleeding episodes per patient.
- Total number of exposure days per patient per year.
- Mean dose of rFVIIIFc per kg per patient per year per treatment regimen.
- Physician's global assessment of response to treatment using a 4-point scale.
- Patient's assessment of response to treatment using a 4-point scale.
- Incidence of AEs and SAEs.
- Surgery endpoints including haemostatic response.
- Patient-reported outcome endpoints including QoL questionnaires.

Approximately 194 patients (144 from 997HA301 and 50 from 8HA02PED) are expected to be eligible for enrolment. The key exclusion criterion for this study is a confirmed high-titre (≥ 5.0 Bethesda unit (BU)/mL) inhibitor test result. Patients will continue in the study for up to 4 years or until rFVIIIFc is commercially available. It is expected that each patient will attain a minimum of 50 exposure days during the study.

As of 7 January 2013, 150 patients from 997HA301 were enrolled and received at least one dose of rFVIIIFc, 95 of whom completed the first 6 month safety visit. One patient had discontinued due to a protocol violation. Of the 150 enrolled patients, 11 (7%) were 12 to 17 years of age. The median age was 31.0 years (range 13 - 66) and the majority were White (65%). No patients were enrolled from the paediatric study 8HA02PED.

No AE data have been analysed at the January 2013 y6y6cut-off. There were no deaths. There were 10 SAEs reported by 8 patients all of which were considered unrelated to study treatment. There were no AEs of special interest (inhibitors, anaphylaxis, serious hypersensitivity or thrombotic events). No unique safety features were identified in the adolescent group.

8.2. Pivotal studies that assessed safety as a primary outcome

None submitted.

8.3. Patient exposure

Patient exposure data are limited to the pivotal Phase III study 997HA301. The extension studies 8HA01EXT and 8HA02PED are still ongoing and the PKstudy CPP-12-026 contributed less than 0.2% of the overall exposure data. Exposure in the pivotal study is shown in Table 8 and Table 9. A total of 164 patients received at least one dose of rFVIIIFc for a median duration of 30.5 weeks (range < 1 to 54 weeks). Overall, 97.0%, 89.0%, 14.0% and 3.7% of patients received treatment for at least 13, 26, 39 and 52 weeks, respectively. The median total exposure days (EDs) for all dosed patients was 57 (range 1 to 123), with 111 patients having ≥ 50 EDs. The mean total number of injections given was 57 (range 1 to 136).

Table 8: Duration of dosing with rFVIIIFc safety analysis set.

	Arm 1 (N=110)	Arm 2 (N=24)	Arm 3 (N=23)	Total (N=165)
Cumulative number of weeks on rFVIIIFc (a)				
At least 13 weeks	116 (99.1%)	20 (83.3%)	23 (100.0%)	159 (97.0%)
At least 26 weeks	112 (95.7%)	16 (66.7%)	19 (70.3%)	146 (89.0%)
At least 39 weeks	23 (19.7%)	0	0	23 (14.0%)
At least 52 weeks	6 (5.1%)	0	0	6 (3.7%)
Total weeks on rFVIIIFc				
n	117	24	23	164
Mean (SD)	34.2 (8.15)	24.4 (9.73)	28.1 (3.80)	31.9 (8.78)
Median	32.1	28.9	28.9	30.5
Min, Max	5, 54	<1, 39	15, 32	<1, 54

NOTE 1: Percentages are based on the number of subjects who received rFVIIIFc in each treatment arm or overall. Subject 581-002 (Arm 1) received only Advate.
2: Time on rFVIIIFc refers to the length of time from the first rFVIIIFc PK dose through the last day of the efficacy period.
(a) A subject can appear in more than one category.

Table 9: Exposure data. Summary of injections and days of exposure to rFVIIIFc. Safety analysis set.

	Arm 1 (N=110)	Arm 2 (N=24)	Arm 3 (N=23)	Surgery subgroup (N=9)	Total (N=165)
Total exposure days (a)					
<50	9 (7.7%)	23 (95.8%)	21 (91.3%)	1 (11.1%)	53 (32.3%)
>=50	108 (92.3%)	1 (4.2%)	2 (8.7%)	8 (88.9%)	111 (67.7%)
n	117	24	23	9	164
Mean	67.4	30.0	24.4	79.4	55.9
SD	17.84	14.95	14.86	26.21	24.93
Median	64.0	30.5	21.0	79.0	57.0
Min, Max	16, 123	1, 75	7, 63	35, 123	1, 123
Total number of injections per subject					
n	117	24	23	9	164
Mean	68.9	30.2	24.8	91.7	57.0
SD	19.60	14.99	15.16	32.36	26.26
Median	65.0	30.5	22.0	93.0	57.0
Min, Max	16, 136	1, 75	7, 65	37, 136	1, 136

NOTE 1: Percentages are based on the number of subjects in each treatment arm or overall.
2: Subjects in the surgery subgroup are also counted in the other arm in which they participated. Each subject is counted only once in the total column. Subject 581-002 (Arm 1) received only Advate.
(a) An exposure day is a 24 hour period in which one or more rFVIIIFc injections are given. All injections over the study course are counted.

8.4. Adverse events

8.4.1. All adverse events (irrespective of relationship to study treatment)

8.4.1.1. Pivotal study

A summary of the AEs reported in each of the treatment arms and the three arms combined is shown in Table 10. In the 164 patients in the three arms combined, 65.9% reported at least one AE, 8.5% reported at least one SAE. AEs presented by system organ class (SOC) are shown in Table 11 and by preferred term in Table 12. The SOCs with the highest incidence, reported in ≥10% of patients, were infections and infestations (26.2%), musculoskeletal and connective tissue disorders (18.9%), GI disorders (13.4%), nervous system disorders (13.4%), general disorders and administration site conditions (12.8%), and injury poisoning and procedural complications (11.0%). AEs reported by preferred term in ≥ 3% of the study population were nasopharyngitis (12.2%), arthralgia (7.9%), headache (7.9%), upper respiratory tract infection (URTI) (5.5%), and influenza and pyrexia (3.0% each). A total of 48.8% of patients reported at least one AE on the day or day after an rFVIIIFc injection. The pattern of AEs was similar to that of the whole study period. Four (2.4%) patients developed back pain but these events were not considered to be related to treatment.

Medically important AEs of special interest relevant to the haemophilia population were reported to the sponsor as SAEs whether or not they met SAE criteria.

Table 10: Study 997HA301. Overall summary of treatment emergent adverse events. Safety analysis set.

	Arm 1 (N=118)					
	Advate (a) (N=30)	rFVIIIFc (N=117)	Arm 2 (N=24)	Arm 3 (N=23)	Surgery subgroup (b) (N=9)	Total rFVIIIFc (N=164)
Subjects with at least one TEAE n (%)	3 (10.0%)	80 (68.4%)	18 (75.0%)	10 (43.5%)	4 (44.4%)	108 (65.9%)
Subjects with at least one related TEAE (c) n (%)	0	5 (4.3%)	3 (12.5%)	2 (8.7%)	0	10 (6.1%)
Subjects who discontinued treatment and/or the study due to an AE n (%)	0	1 (0.9%)	3 (12.5%)	0	0	4 (2.4%)
Subjects with at least one TESAE n (%)	0	10 (8.5%)	2 (8.3%)	0	2 (22.2%)	14 (8.5%)
Subjects with at least one related TESAE (c) n (%)	0	0	0	0	0	0
Number of deaths n (%)	0	1 (0.9%)	0	0	0	1 (0.6%)

Table 11. Study 997HA301. Treatment Emergent Adverse Events by MedRA system organ class. Safety analysis set.

System organ class	Arm 1 rFVIIIFc (N=117)		Arm 2 (N=24)		Arm 3 (N=23)		Total rFVIIIFc (N=164)	
Number of subjects with at least one TEAE	80	(68.4%)	18	(75.0%)	10	(43.5%)	108	(65.9%)
Infections and infestations	34	(29.1%)	3	(12.5%)	6	(26.1%)	43	(26.2%)
Musculoskeletal and connective tissue disorders	24	(20.5%)	6	(25.0%)	1	(4.3%)	31	(18.9%)
Gastrointestinal disorders	16	(13.7%)	4	(16.7%)	2	(8.7%)	22	(13.4%)
Nervous system disorders	13	(11.1%)	7	(29.2%)	2	(8.7%)	22	(13.4%)
General disorders and administration site conditions	15	(12.8%)	2	(8.3%)	4	(17.4%)	21	(12.8%)
Injury, poisoning and procedural complications	14	(12.0%)	4	(16.7%)	0		18	(11.0%)
Respiratory, thoracic and mediastinal disorders	9	(7.7%)	4	(16.7%)	1	(4.3%)	14	(8.5%)
Skin and subcutaneous tissue disorders	6	(5.1%)	3	(12.5%)	1	(4.3%)	10	(6.1%)
Investigations	7	(6.0%)	1	(4.2%)	1	(4.3%)	9	(5.5%)
Psychiatric disorders	3	(2.6%)	1	(4.2%)	1	(4.3%)	5	(3.0%)
Vascular disorders	4	(3.4%)	1	(4.2%)	0		5	(3.0%)
Cardiac disorders	3	(2.6%)	0		0		3	(1.8%)
Blood and lymphatic system disorders	2	(1.7%)	0		0		2	(1.2%)
Eye disorders	2	(1.7%)	0		0		2	(1.2%)
Ear and labyrinth disorders	1	(0.9%)	0		0		1	(0.6%)
Hepatobiliary disorders	1	(0.9%)	0		0		1	(0.6%)
Immune system disorders	1	(0.9%)	0		0		1	(0.6%)
Renal and urinary disorders	0		1	(4.2%)	0		1	(0.6%)

NOTE 1: Percentages are based on the number of subjects treated with rFVIIIFc in each arm or overall.
2: Using the MedDRA Version 15.0 dictionary.
3: Subjects are counted once if they report multiple events in the same system organ class.
4: Does not include AEs emergent during the surgical/rehabilitation period.

Table 12: Study 997HA301. Treatment emergent adverse events by preferred term in descending order of incidence (≥ 3%). Safety analysis set.

Preferred term	Arm 1 rFVIIIFc (N=117)		Arm 2 (N=24)		Arm 3 (N=23)		Total rFVIIIFc (N=164)	
Total number of TEAEs	219		46		23		288	
Number of subjects with at least one TEAE	80	(68.4%)	18	(75.0%)	10	(43.5%)	108	(65.9%)
Nasopharyngitis	16	(13.7%)	1	(4.2%)	3	(13.0%)	20	(12.2%)
Arthralgia	10	(8.5%)	2	(8.3%)	1	(4.3%)	13	(7.9%)
Headache	5	(4.3%)	6	(25.0%)	2	(8.7%)	13	(7.9%)
Upper respiratory tract infection	6	(5.1%)	0		3	(13.0%)	9	(5.5%)
Influenza	5	(4.3%)	0		0		5	(3.0%)
Pyrexia	3	(2.6%)	1	(4.2%)	1	(4.3%)	5	(3.0%)

NOTE 1: Percentages are based on the number of subjects treated with rFVIIIFc in each arm or overall.
Subject 581-002 (Arm 1) received only Advate.
2: Using the MedDRA Version 15.0 dictionary.
3: Subjects are counted once if they report multiple events in the same preferred term.
4: Does not include AEs emergent during the surgical/rehabilitation period.

· Development of Inhibitor.

No patients developed an inhibitor during the study (defined as a neutralising antibody value ≥ 0.6 BU/mL).

· Allergic reaction.

No SAEs of allergic reaction, anaphylaxis, or serious hypersensitivity events were reported during the study.

· Thrombotic events:

No SAEs of thrombotic events were reported (IV injection site thrombophlebitis was excluded).

· Suspected transmission of an infectious agent.

No cases were reported during the study.

· Infection events.

In the overall safety set of 164 patients, 43 (26.2%) experienced at least one AE in the infections and infestations SOC as summarised above. The events were all common in the general haemophilia population and in the setting of co-morbidities such as HIV infection.

· Bleeding Episodes.

The protocol specified that bleeding episodes were not reported as AEs unless they met SAE criteria. There was one bleeding SAE during the study; a hip haemarthrosis considered unrelated to rFVIIIFc treatment.

An analysis of AEs was performed in subgroups defined by age, BMI, race, baseline HIV/HCV status, history of advanced hepatic disease, and extrinsic factors such as use of IV ports and geographical location of the patients. Overall, there was no unusual pattern in the distribution and type of AEs in the adolescent and adult patient subgroups (only one patient was elderly). Similarly, there were no apparent differences related to BMI or race. As might be expected, the incidence of AEs was somewhat higher in patients with positive HIV/HCV status (70.9% in the HIV/HCV subgroup compared with 60.3% in the non-HIV/HCV subgroup). Three patients had advanced hepatic disease and none of the AEs reported in these patients was remarkable. No meaningful geographic differences were observed.

8.4.1.2. Other studies

AEs recorded in 8HA01EXT at the January 2013 cut-off date have not yet been analysed.

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

8.4.2.1. Pivotal study

The great majority of AEs were judged unrelated to rFVIIIFc treatment by the investigators. AEs judged to be drug related occurred in 10 (6.1%) of the total study population. The AEs reported as related were malaise and arthralgia (each reported in two patients), bradycardia, lower abdominal pain, chest pain, feeling cold, feeling hot, procedural hypotension, brain natriuretic peptide (BNP) increased, joint swelling, myalgia, dizziness, dysgeusia, headache, cough, rash, vascular pain after injection, and hypertension (each reported in one patient).

8.4.2.2. Other studies

In 8HA01EXT, treatment-related AEs have not yet been analysed at the January 2013 cut-off date.

8.4.3. Deaths and other serious adverse events

8.4.3.1. Pivotal study

There was one death caused by suicide (an overdose of multiple drugs of addiction). In the total study population, SAEs were reported in 12 (7.3%) patients. Three (1.8%) patients experienced at least one SAE in the injury, poisoning and procedural complication SOC, three (1.8%) patients in the musculoskeletal and connective tissues SOC, two (1.2%) patients in the gastrointestinal SOC. The other SOCs with one (0.6%) patient who experienced an SAE were cardiac disorders; psychiatric disorders; renal and urinary disorders; respiratory, thoracic and mediastinal disorders; and vascular disorders. None of the SAEs was considered to be related to rFVIIIFc by the investigators.

8.4.3.2. Other studies

In 8HA01EXT at the cut-off point of 07 January 2013, 10 SAEs were reported in 8 patients: hydrocephalus, head injury, spinal osteoarthritis, haemorrhagic gastritis, joint dislocation, dehydration, device dislocation, post-procedural haemorrhage, depression and traumatic haematoma. None of the events was considered to be drug related.

8.4.4. Discontinuation due to adverse events

8.4.4.1. Pivotal study

Overall, four patients prematurely discontinued rFVIIIFc due to AE or death: one case each of related arthralgia, related rash, unrelated femur fracture, and suicide by drug overdose.

8.4.4.2. Other studies

In 8HA01EXT, no discontinuations due to AEs have been recorded at the January 2013 cut-off date.

8.5. Laboratory tests

Summary statistics of actual values and change from baseline for liver function, renal function, electrolytes and other parameters for the combined and individual treatment arms were provided. No clinically meaningful changes were observed in the mean actual value or mean change from baseline over time in any of the blood chemistry parameters in any treatment arm. A summary of the number and percentage of patients with potentially clinically significant abnormal post-baseline blood chemistry values is shown in Table 13. In 8HA01EXT, laboratory parameters had not been analysed at the January 2013 cut-off date.

Table 13: Study 997HA301. Summary of potentially significant abnormalities: blood chemistry. Safety analysis set.

Laboratory Test	Threshold	Arm 1 (N=118) n/m eval (%)	Arm 2 (N=24) n/m eval (%)	Arm 3 (N=23) n/m eval (%)	Total (N=165) n/m eval (%)
Liver					
Alanine Aminotransferase	>=3 x ULN	4/117 (3.4%)	0/24	0/23	4/164 (2.4%)
Aspartate Aminotransferase	>=3 x ULN	4/117 (3.4%)	1/24 (4.2%)	0/23	5/164 (3.0%)
Alkaline phosphatase	>=3 x ULN	0/117	0/24	0/23	0/164
Total bilirubin	>=34.2 umol/L	3/117 (2.6%)	0/24	2/23 (8.7%)	5/164 (3.0%)
Renal					
Blood urea nitrogen	>=10.7 mmol/L	1/117 (0.9%)	1/24 (4.2%)	0/23	2/164 (1.2%)
Creatinine	>=176.8 umol/L	0/117	0/24	0/23	0/164
Electrolytes					
Sodium	<=126 mmol/L	0/117	0/24	0/23	0/164
	>=156 mmol/L	1/117 (0.9%)	0/24	0/23	1/164 (0.6%)
Potassium	<=3 mmol/L	0/117	0/24	0/23	0/164
	>=6 mmol/L	0/117	0/24	0/23	0/164
Chloride	<=90 mmol/L	1/117 (0.9%)	0/24	0/23	1/164 (0.6%)
	>=118 mmol/L	0/117	0/24	0/23	0/164

8.5.1. Liver function

8.5.1.1. Pivotal study

Potentially clinically significant elevations in ALT (≥ 3xULN), aspartate aminotransferase (AST) (≥ 3xULN) and total bilirubin (34.2 µmol/L) occurred in 2.4%, 3.0% and 3% of the patients, respectively. None of the patients had a combination of elevated ALT and/or AST with elevated bilirubin. In the 11 patients with significant liver function test (LFT) abnormalities, all had pre-existing high LFTs or a history of hepatitis.

8.5.2. Kidney function

8.5.2.1. Pivotal study

Modest elevations in blood urea nitrogen (BUN) occurred in 2/164 (1.2%) patients. There were no significant increases in serum creatinine (≥ 176.8 µmol/L) during the study.

8.5.3. Other clinical chemistry

8.5.3.1. Pivotal study

No significant treatment emergent abnormalities in any other clinical chemistries were recorded during the study.

8.5.4. Haematology

8.5.4.1. Pivotal study

No clinically meaningful changes were observed in the mean actual value or mean change from baseline over time in any treatment arm. A summary of the number and percentage of patients with a shift from baseline to low or high post-baseline value is shown in Table 14. An upwards shift for haematocrit occurred in 11.5% of patients but overall there were no meaningful shifts in haematology data.

Table 14: Study 997HA301. Summary of shifts from baseline to minimum/maximum post baseline value for laboratory results: haematology. Safety analysis set.

Laboratory test	Shift to	Arm 1 (N=110) n/m eval (%)	Arm 2 (N=24) n/m eval (%)	Arm 3 (N=23) n/m eval (%)	Total (N=165) n/m eval (%)
Leukocytes	Low	9/109 (8.3%)	1/ 21 (4.8%)	3/ 22 (13.6%)	13/152 (8.6%)
	High	7/114 (6.1%)	2/ 22 (9.1%)	3/ 23 (13.0%)	12/159 (7.5%)
Lymphocytes	Low	1/104 (1.0%)	1/ 22 (4.5%)	1/ 21 (4.8%)	3/147 (2.0%)
	High	0/104	0/ 22	0/ 21	0/147
Neutrophils	Low	8/ 99 (8.1%)	1/ 21 (4.8%)	0/ 20	9/140 (6.4%)
	High	7/102 (6.9%)	2/ 20 (10.0%)	2/ 21 (9.5%)	11/143 (7.7%)
Monocytes	Low	5/104 (4.8%)	0/ 22	1/ 21 (4.8%)	6/147 (4.1%)
	High	3/104 (2.9%)	0/ 21	1/ 21 (4.8%)	4/146 (2.7%)
Eosinophils	Low	0/104	0/ 22	0/ 21	0/147
	High	8/ 95 (8.4%)	3/ 22 (13.6%)	2/ 20 (10.0%)	13/137 (9.5%)
Basophils	Low	0/104	0/ 22	0/ 21	0/147
	High	0/104	0/ 22	0/ 21	0/147
Erythrocytes	Low	6/105 (5.7%)	3/ 23 (13.0%)	1/ 23 (4.3%)	10/151 (6.6%)
	High	8/109 (7.3%)	1/ 22 (4.5%)	2/ 18 (11.1%)	11/149 (7.4%)
Hemoglobin	Low	7/114 (6.1%)	2/ 24 (8.3%)	2/ 22 (9.1%)	11/160 (6.9%)
	High	5/108 (4.6%)	0/ 24	0/ 22	5/154 (3.2%)
Hematocrit	Low	3/116 (2.6%)	0/ 24	1/ 23 (4.3%)	4/163 (2.5%)
	High	13/111 (11.7%)	3/ 24 (12.5%)	2/ 21 (9.5%)	18/156 (11.5%)
Platelet counts	Low	4/114 (3.5%)	1/ 21 (4.8%)	3/ 23 (13.0%)	8/158 (5.1%)
	High	0/116	1/ 24 (4.2%)	1/ 22 (4.5%)	2/162 (1.2%)

8.5.5. Electrocardiograph

8.5.5.1. Pivotal study

The study protocol did not include baseline or follow-up ECGs.

8.5.6. Serum immunoglobulin concentrations

8.5.6.1. Pivotal study

No clinically meaningful changes were observed in the mean actual value or mean change from baseline over time in the total immunoglobulin G (IgG) or any of the four IgG subclasses in any treatment arm.

8.5.7. Vital signs

8.5.7.1. Pivotal study

Vital signs were measured at Screening and before and 30 minutes after injection of the first dose of rFVIIIFc. There were no clinically meaningful or consistent trends in vital signs.

8.6. Post-marketing experience

rFVIIIFc is not approved or marketed in any country.

8.7. Safety issues with the potential for major regulatory impact

8.7.1. Liver toxicity

No issues identified.

8.7.2. Haematological toxicity

No issues identified.

8.7.3. Serious skin reactions

No issues identified.

8.7.4. Cardiovascular safety

No issues identified.

8.7.5. Unwanted immunological events

No issues identified.

8.8. Other safety issues

8.8.1. Safety in special populations

No studies in special populations have been conducted. An analysis of AEs in patient subgroups defined by age, BMI, race, baseline HIV/HCV status, history of advanced hepatic disease, and extrinsic factors such as use of IV ports and geographical location of the patients is discussed in section 8.4.1.1. Overall, there was no unusual pattern in the distribution and type of AEs in any patient subgroup.

8.8.2. Safety related to drug-drug interactions and other interactions

No formal drug-drug interaction studies were conducted as they are generally inapplicable for biologic therapies. No observations in the pivotal study suggested a potential drug-drug interaction.

8.9. Evaluator's overall conclusions on clinical safety

In general, rFVIIIFc was well tolerated. In the single pivotal Phase III study, 164 previously treated adult and adolescent patients with haemophilia A received at least one dose of rFVIIIFc. The study was sufficient in size to adequately assess the risk of inhibitor formation and very common or common AEs. A total of 146 patients have been treated for at least 26 weeks and a long-term extension study is on-going. There was no placebo control group but the types and incidence of AEs were consistent with those expected in the haemophilia population. With the exception of arthralgia recorded in 7.9% of patients, the most common AEs [nasopharyngitis (12.2%), headache (7.9%) and URTI (5.5%)] are commonly reported in the general population. No deaths or SAEs were considered related to rFVIIIFc treatment by Investigators. The pattern of infections was unremarkable and there was no evidence of immune compromise or increased risk of infection. The AE profile in patients with underlying HIV/HCV was similar to the rest of the patient population. Safety in adolescents appeared similar to that of the adults and there appeared to be no effects related to race, BMI or geographic region. There were no meaningful patterns or trends in clinical chemistry, haematology or vital signs. No patient developed an inhibitor or other AEs of special interest. Target organ toxicity is not a feature of biologics but there were no cases of anaphylaxis or hypersensitivity reactions. In keeping with the orphan population, limited patient numbers have been treated but no safety signals have been detected to date.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of Eloctate in the proposed usage are:

- Effective control of bleeding with 87.3% of acute bleeds controlled with a single injection.
- Effective as routine individualised prophylaxis with 92% reduction in annualised bleeding rates compared with episodic (on-demand) treatment.
- Effective as once weekly prophylaxis with 76% reduction in annualised bleeding rates compared with episodic (on-demand) treatment.
- Effective for peri-operative management with 100% excellent or good haemostasis.
- A long half-life (18.97 hours), 1.53-fold longer than Advate (rFVIII).
- Reduced dosing frequency. Almost 90% of patients had a history of requiring three or more prophylaxis injections/week of FVIII before the study, compared with an average dosing interval of 3 days or longer on rFVIIIFc.
- Clear dosing recommendations based on population PK data.
- No cases of inhibitor formation in 110 patients with at least 50 EDs (upper bound of 95% CI was 3.3%).
- Fully recombinant with no human or animal additives.
- Well tolerated with no anaphylaxis or hypersensitivity reactions to date.

9.2. First round assessment of risks

The risks of Eloctate in the proposed usage are:

- The safety database includes only 180 patients aged ≥ 12 years. Uncommon AEs such as hypersensitivity reactions may not have been detected.
- Long-term safety has not been established.
- No safety data in children aged < 12 years.
- No safety data in PUPs (at higher risk of inhibitor development).
- Risk of severe hypersensitivity reactions not yet known.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of Eloctate, given the proposed usage, is favourable.

10. First round recommendation regarding authorisation

Authorisation is recommended for the use of Eloctate in adults and children (≥ 12 years) with haemophilia A for control and prevention of bleeding episodes; routine prophylaxis to prevent or reduce the frequency of bleeding episodes; and peri-operative management (surgical prophylaxis). Approval is subject to satisfactory response to questions raised in section 11.

The TGA delegate has expressed concern about whether the data support an indication that encompasses adult and/or adolescent patients. The EMA Guidelines (2000 and 2009) are silent on adolescents and recommend patient studies in an inclusive population aged ≥ 12 years.

Although there is no specific requirement, the safety and efficacy study included 13 adolescent patients whose response was similar to that of the adult population.

11. Clinical questions

11.1. Pharmacokinetics

Would the sponsors suggest why all the reported bleeding events in the PK study 998HA101 occurred in the rFVIIIFc group and none in the Advate group.

11.2. Pharmacodynamics

No questions.

11.3. Efficacy

In the pivotal study, 26.8% of patients had major informed consent 'issues'. Please clarify and provide assurance that the study was performed to full GCP and was adequately monitored.

11.4. Safety

No questions.

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

Sponsor responses were taken into account in the Delegate's overview. See AusPAR *Overall conclusion and risk/benefit assessment.*

13. Second round benefit-risk assessment

Not Applicable.

14. Second round recommendation regarding authorisation

Not Applicable.

15. References

1. CPMP/BPWG/1561/99. Note for guidance on the clinical investigation of recombinant factor VIII and IX products
2. EMA/CHMP/BPWP/144533/2009. Guideline on the clinical investigation of recombinant and human plasma-derived factor VII products.
3. Bjorkman S, et al. *J Thromb Haemost* 2010, 8: 730-36
4. Srivastava A, et al. Guidelines for management of haemophilia. *Haemophilia* 2013, 19: e1-e47

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
http://www.tga.gov.au