Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Lonoctocog alfa

Proprietary Product Name: Afstyla

Sponsor: CSL Behring Australia Pty Ltd

July 2017

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.
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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
ABR	Annualised bleeding rate
AE	Adverse Event
AESI	Adverse event of special interest
ALT	Alanine Transaminase
AsBR	Annualised spontaneous bleeding rate
AST	Aspartate Transaminase
AUC	Area Under the Concentration vs. Time Curve
BUN	Blood Urea Nitrogen
CHO	Chinese hamster ovary
CI	Confidence interval
ChS	Chromogenic substrate (assay)
CL	Clearance
Cmax	Maximum Concentration
DBP	Diastolic blood pressure
dL	Decilitre
ECG	Electrocardiograph
ED	Exposure day
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
FVIII	Factor VIII
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonisation

Abbreviation	Meaning
IU	International Units
kDa	Kilodaltons
kg	kilogram
LDH	Lactate Dehydrogenase
LFTs	Liver Function Tests
LLOQ	Lower limit of quantification
OS	One-stage (assay)
pd-FVIII	Plasma-derived factor VIII
PI	Product Information
PK	Pharmacokinetics
PP	Per protocol
PTP	Previously Treated Patient
PUP	Previously Untreated Patient
rFVIII	Recombinant factor VIII
rVIII-SingleChain	Recombinant factor VIII Single Chain (Lonoctocog alfa)
SAE	Serious Adverse Event
SBP	Systolic blood pressure
SMQ	Standardised MedDRA query
TEAE	Treatment-emergent adverse event
TGA	Therapeutic Goods Administration
T_{max}	Time of maximum concentration
V_{ss}	Volume of distribution at steady state
vWF	von Willebrand factor
WFH	World Federation of Haemophilia

1. Introduction

This is a full submission to register Afstyla (lonoctocog alfa) as a new biological entity.

Lonoctocog alfa is a form of recombinant coagulation factor VIII. It differs from endogenous factor VIII in that a segment of the molecule (most of the B-domain and 4 amino acids of the adjacent *a3* domain) has been removed. It is produced in Chinese hamster ovary (CHO) cells.

The proposed indication is:

> *'Afstyla is indicated in all patients 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)'.*

The proposed product is a lyophilised powder, to be reconstituted with water for injections (WFI) for intravenous injection. 8 strengths are proposed: 250, 375, 500, 1000, 1500, 2000, 2500 and 3000 IU.

Proposed dosage varies according to the clinical scenario. Dosages for the treatment of haemorrhage and use in surgery are calculated using the following formula:

> Dose (IU) = body weight (kg) x desired FVIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL).

Recommended doses are summarised in the following table taken from the draft product information.

Table 1. Recommended doses as summarised in the draft PI

Degree of haemorrhage	**FVIII level required (% or IU/dL)**	**Frequency of Doses (hours)**
Early haemarthrosis muscle bleeding or oral bleeding	20–40	Repeat injection every 12–24 hours until the bleeding is resolved.
More extensive haemarthrosis muscle bleeding or haematoma	30–60	Repeat injection every 12–24 hours until the bleeding is resolved.
Life-threatening haemorrhages	60–100	Repeat injection every 8–24 hours until bleed is resolved.
Control and prevention of bleeding in the perioperative setting	**FVIII level required (% (IU/dL)**	**Frequency of doses (hours)/Duration of therapy (days)**
Minor surgery e.g. (including tooth extraction)	30–60	Repeat injection every 24 hours for at least 1 day, until healing is achieved.
Major surgery	80–100 (pre- and postoperative)	Repeat injection every 8–24 hours until adequate wound healing, then continue therapy for at least another 7 days to maintain a FVIII activity of 30–60% (IU/dL).

For prophylaxis of haemorrhage, the proposed starting dose is 20 to 50 IU/kg administered 2 to 3 times weekly. Subsequent dose is to be adjusted according to the patient's response.

2. Clinical rationale

2.1. Background and clinical rationale

Congenital haemophilia A is a hereditary disorder caused by a deficiency or dysfunction of coagulation Factor VIII (FVIII). The gene for FVIII is located on the X chromosome, and the disorder is inherited as an X-linked recessive condition. Therefore, most subjects with haemophilia A are males.[1]

The clinical manifestations of haemophilia are due to haemorrhage. The disorder can be classified as mild (plasma FVIII levels 5 to < 40% of normal), moderate (1 to 5% of normal) and severe (< 1% of normal).[2] Subjects with severe haemophilia A suffer from recurrent spontaneous bleeding, typically into joints and muscles. Repeated haemorrhages into joints can result in a chronic arthropathy.[3]

The 2013 to 2014 Annual Report of the Australian Bleeding Disorders Registry estimated that there were 2,181 subjects in Australia with haemophilia A.[4]

Treatment of haemophilia A is based on the use of replacement factor VIII products. Replacement therapy may be 'on demand' where treatment is given when a haemorrhage occurs, or prophylactic factor VIII is administered at regular intervals in an attempt to prevent the onset of haemorrhage.

Endogenous FVIII circulates in plasma as a molecule with 2 chains connected by a disulphide bond: a heavy chain at the NH_2 end (MW around 90 to 200 kDa) and a light chain at the COOH end (MW around 80 kDa). The molecule is also organised into a series of domains which are labelled (from the NH_2 terminal end) as A1, *a1*, A2, *a2*, B, *a3*, A3, C1 and C2. The *a1*, *a2*, and *a3* domains are short spacers domains and are referred to as the acidic regions.[5]

In the lonoctocog alfa molecule, most of the B-domain and 4 amino acids of the adjacent *a3* region have been removed (amino acids 765 to 1652 of full length FVIII). The cleavage site present in wildtype FVIII between the heavy and light chains (that is, between the B-domain and the *a3* region) is also removed, and therefore lonoctocog is expressed as a single chain FVIII molecule. The new linkage of the heavy and light chains of FVIII also introduces a new N-glycosylation site. The lonoctocog molecule contains 1444 amino acids and has a molecular weight of approximately 170 kDa.

According to the sponsor these modifications were made in order to:

- Avoid potential dissociation of the heavy and light chains of non-activated FVIII;
- Reduce the chance of potential neoantigenicity by making use of the shielding effect of the new N-glycan side chain formed at the linkage site;
- Achieve high expression yield of rFVIII: and
- Obtain high process yield due to the stable single-chain rFVIII construct.

In addition, it was discovered that lonoctocog had a stronger affinity for its natural carrier protein von Willebrand factor, compared to other recombinant FVIII molecules. As von

[1] Mannucci P and Tuddenham E. The hemophilias-from royal genes to gene therapy. N Engl J Med. 2001; 344 (23): 1773-9.
[2] World Federation of Hemophilia. Guidelines for the Management of Hemophilia (2nd edition). 2012.
[3] Peyvandi F, et al. The past and future of haemophilia: diagnosis, treatments, and its complications. Lancet. 2016; Published online: February 17, 2016.
[4] National Blood Authority Australia. Australian Bleeding Disorders Registry. Annual Report 2013-2014.
[5] Lenting P et al. The Life Cycle of Coagulation Factor VIII in View of Its Structure and Function. Blood. 1998; 92 (11): 3983-3996.

Willebrand factor binds FVIII and protects it from early proteolysis, the sponsor claims that this property results in an improved PK profile.

After activation of lonoctocog alfa, it has an amino acid sequence identical to that of activated FVIII formed from endogenous, full-length FVIII.

In the submission documentation, the sponsor generally referred to the product as 'rVIII-SingleChain'. For consistency, this term will also be used in this document.

2.2. Guidance

The following EMA guidelines, which have been adopted by the TGA, are considered relevant to the current application:

1. Guideline on the Clinical Investigation of the Pharmacokinetics of Therapeutic Proteins (CHMP/EWP/89249/2004); 2007
2. Guideline on clinical investigation of recombinant and human plasma-derived factor VIII products (EMA/CHMP/BPWP/144533/2009); 2011

The 2011 EMA guideline on factor VIII products has recently been updated.[6] However, this revised version did not come into effect in the EU until May 2016, after the sponsor had completed the pivotal studies contained in this submission. At the time of writing, the 2016 revision had not been adopted by the TGA.

Compliance with these guidelines will be considered in the relevant sections of this report.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

- 1 pivotal Phase I/III clinical trial conducted in adults and adolescents (Study 1001) that provided data on pharmacokinetics, efficacy and safety;
- 1 pivotal Phase III clinical trial conducted in children aged < 12 years (Study 3002) that provided data on pharmacokinetics, efficacy and safety;
- An interim study report on an ongoing open label extension trial (Study 3001) that provided safety data only.
- 1 population pharmacokinetic analysis.
- A Clinical Overview, Summary of Biopharmaceutics, Summary of Clinical Pharmacology, Summary of Clinical Efficacy and Summary of Clinical Safety.

3.2. Paediatric data

The submission included paediatric pharmacokinetic, efficacy and safety data.

[6] European Medicines Agency. Guideline on clinical investigation of recombinant and human plasma-derived factor VIII products (EMA/CHMP/BPWP/144533/2009 rev 1); 2016.

3.3. Good clinical practice

All clinical study reports included an assurance that the studies had been conducted in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice guidelines and the Declaration of Helsinki.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

The 2 pivotal studies in this submission (Studies 1001 and 3002) provided PK data. Table 2 below shows the studies relating to each pharmacokinetic topic.

Table 2. Submitted pharmacokinetic studies

PK topic	Study ID	Subtopic	*
PK in haemophilia A subjects	1001	Population: Adults and adolescents	
		General PK (Single dose)	*
		General PK (Repeat dose)	*
		Bioequivalence[1] (Single dose)	
	3002	Population: Children aged < 12 years	
		General PK (Single dose)	
Population PK analyses		Haemophilia A subjects	*

* Indicates the primary aim of the study; 1) Bioavailability compared with a registered rFVIII product (Advate)

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. Physicochemical characteristics of the active substance

The following information is derived from the sponsor's summaries. rVIII-SingleChain is a form of recombinant coagulation factor VIII in which most of the B-domain and 4 amino acids of the adjacent *a3* domain have been removed. It contains 1444 amino acids and has a molecular weight of approximately 170 kilodaltons. It is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) cell line.

4.2.2. Pharmacokinetics in haemophilia A subjects

4.2.2.1. Assays for FVIII activity

As recommended by the relevant EMA guideline, FVIII activity was used to measure rVIII-SingleChain PK. rVIII-SingleChain antigen levels were not measured. 2 assays are commonly used to measure FVIII activity in plasma, the chromogenic substrate (ChS) assay and the one stage (OS) assay. Early in the development of rVIII-SingleChain it was recognised that there was a discrepancy between these 2 assays in the measurement of FVIII activity produced by rVIII-SingleChain. The OS assay gave results that were lower than the results produced by the ChS assay. Preclinical data indicated that the ChS assay more accurately predicted effectiveness and hence the ChS assay was chosen to assign potency for the product.

In the clinical PK studies both the ChS and OS were used to assess FVIII activity in plasma. The OS assay gave results that were approximately 45% lower than the results produced by the ChS assay.

The sponsor recommends the use of the ChS assay, if available, for assessing FVIII activity in plasma. However, the OS assay is commonly used in clinical practice for assessing FVIII activity in haemophilia A subjects. The sponsor is therefore proposing that results obtained with the OS assay can be corrected (multiplied by a factor of 1.8) to estimate the results that would be obtained with the ChS assay.

The following summary is based on results obtained with the ChS assay.

4.2.2.2. Absorption

rVIII-SingleChain is only administered intravenously and by definition has 100% absorption and bioavailability. T_{max} occurred at the time of the first plasma sample was taken.

Incremental recovery

In adults and adolescents: mean incremental recovery after a single dose of 50 IU/kg rVIII-SingleChain was 2.24 IU/dL per IU/kg. This value was similar to that obtained with Advate (2.32 IU/dL per IU/kg).

In children aged < 12 years: incremental recovery for rVIII-SingleChain was lower than in adults (1.60 IU/dL per IU/kg for children aged < 6 years and 1.66 IU/dL per IU/kg for children aged 6 and 12 years).

Comment: According to the WFH guidelines, in the absence of an inhibitor, each unit of FVIII per kilogram of body weight infused intravenously will raise the plasma FVIII level by approximately 2 IU/dl.[2] The results obtained in Study 1001 are therefore consistent with other FVIII products. Reduced incremental recovery in children has been described for other recombinant FVIII products.

4.2.2.3. Bioavailability

Bioequivalence of different dosage forms and strengths

Study 1001 compared the PK of FVIII activity following use of 3000 IU or 250 IU vials. Although not a formal bioequivalence study, the results suggested that the 2 vial strengths produced comparable PK.

Bioequivalence to relevant registered products

Study 1001 compared the PK of FVIII activity following administration of rVIII-SingleChain and another recombinant FVIII product that is registered in Australia (Advate, Octocog alfa). Following single doses of 50 IU/kg of both products, rVIII-SingleChain was associated with a 37% higher AUC compared to Advate.

Dose proportionality

Dose proportionality was not studied.

Bioavailability during multiple dosing

Study 1001 compared the PK of FVIII activity following administration of rVIII-SingleChain at baseline and again after 3 to 6 months of treatment (on demand or prophylaxis). The results suggested that chronic administration was not associated with clinically significant alterations in PK.

4.2.2.4. Distribution

Volume of distribution

In adults and adolescents: values for volume of distribution at steady state (V_{ss}) were approximately 50 to 60 mL/kg, equating to 3.5 to 4.2 L in a 70 kg subject. In the population PK analysis, the predicted volumes of distribution for a typical subject (weight 68 kg) were 3.36 L for central volume and 0.265 L for peripheral volume.

In children aged < 12 years: V_{ss} was higher than in adults (71.0 mL/kg for children aged < 6 years and 67.1 mL/kg for children aged 6 and 12 years).

Other distribution parameters

There were no clinical data submitted on plasma protein binding, erythrocyte distribution or tissue distribution.

Comment: The guideline on PK of therapeutic proteins adopted by the states that *'... binding capacity to plasma proteins should be studied when considered relevant'*.[7] It contains no recommendations regarding the need to measure distribution to tissues. The EMA guideline on factor VIII products also does not require investigation of these parameters.[6] The absence of data on other distribution parameters is therefore not considered a deficiency in the submission.

4.2.2.5. Metabolism and excretion

Routes of metabolism and excretion

There were no clinical data in the submission regarding the routes of metabolism and excretion of rVIII-SingleChain.

Comment: According to the EMA guideline on PK of therapeutic proteins, the elimination of large proteins can be predicted to occur through catabolism by proteolysis. The absence of data on metabolism and excretion is therefore not considered a deficiency.

Clearance

In adults and adolescents: following single intravenous doses of rVIII-SingleChain, clearance ranged from 2.64 to 3.15 mL/hr per kg. This equates to 3.08 to 3.68 mL/min for a 70 kg individual. These values were lower than the clearance value observed for Advate (3.68 mL/hr per kg or 4.29 mL/min). In the population PK analysis, for a 68 kg subject, the predicted value for clearance was 2.12 dL/hr (3.18 mL/min).

In children aged < 12 years: clearance was higher than in adults (5.07 mL/hr per kg for children aged < 6 years and 4.63 mL/hr per kg for children aged 6 and 12 years).

[7] Guideline on the Clinical Investigation of the Pharmacokinetics of Therapeutic Proteins (CHMP/EWP/89249/2004); 2007

Half-life

In adults and adolescents: following single intravenous doses of rVIII-SingleChain, half-life was in the range of 12.9 to 14.5 hours. These values were similar to the half-life value observed for Advate 13.3 hours .

In children: the observed mean half-life was lower than that observed in adults (10.4 hours for children aged < 6 years and 10.2 hours for children aged 6 and 12 years).

Comment: According to the WFH guidelines the half-life of FVIII is approximately 8 to 12 hours.[2] The observed half-life of FVIII activity following rVIII-SingleChain administration is consistent with this value.

4.2.2.6. Intra- and inter-individual variability of pharmacokinetics

Variability in PK parameters was modest with values for co-efficient of variation generally being < 35%. In the population PK analysis, the only covariates with a significant effect on rVIII-SingleChain PK were body weight and baseline vWF concentration.

4.2.3. Pharmacokinetics in special populations

4.2.3.1. Pharmacokinetics in subjects with impaired hepatic function

No dedicated clinical studies were conducted in subjects with hepatic impairment. In the population PK analysis baseline AST level, ALT level or hepatitis positivity had no significant effect on rVIII-SingleChain PK.

4.2.3.2. Pharmacokinetics in subjects with impaired renal function

No dedicated clinical studies were conducted in subjects with renal impairment. In the population PK analysis baseline creatinine clearance had no significant effect on rVIII-SingleChain PK.

4.2.3.3. Pharmacokinetics according to age

In the Summary of Clinical Pharmacology for the submission the sponsor presented a summary of PK data based on age. For a dose of 50 IU/kg, children demonstrated higher clearance and a larger volume of distribution than adults. Consistent with increased clearance, children had lower C_{max}, AUC and incremental recovery.

The population PK analysis did not detect a significant effect of age (in addition to bodyweight) on rVIII-SingleChain PK. The sponsor commented that this was likely to be due to the strong correlation between age and total body weight in children.

4.2.3.4. Pharmacokinetics according to race

The population PK analysis did not detect a significant effect of race on rVIII-SingleChain PK.

4.2.4. Pharmacokinetic interactions

No data were submitted on PK interactions.

4.3. Evaluator's overall conclusions on pharmacokinetics

The PK of rVIII-SingleChain have been adequately characterised, given the rarity of haemophilia A and the fact that rVIII-SingleChain is a large protein administered IV (intravenous). The data generated meet the requirements for PK data laid down in the relevant EMA guidelines.

The data demonstrate that administration of rVIII-SingleChain is associated with restoration of FVIII activity in plasma in subjects with severe FVIII deficiency. The FVIII activity levels achieved are modestly increased compared to another recombinant FVIII product registered in Australia (Advate). Compared to adults, children have increased clearance of rVIII-SingleChain and a higher volume of distribution, and as a result achieve lower plasma FVIII activity levels.

5. Pharmacodynamics

FVIII activity was measured in the 2 pivotal studies that were submitted. In haemophilia A studies this is considered to be a pharmacokinetic endpoint and results have therefore been described above in Section 4: Pharmacokinetics (above) of this report. There were no other PD data submitted.

6. Dosage selection for the pivotal studies

In the 2 pivotal efficacy studies, the dose chosen for each patient was based on the 2012 WFH Guidelines, the previous FVIII dose used for the patient and any available PK data.[2]

7. Clinical efficacy

7.1. Pivotal efficacy studies

7.1.1. Study 1001

7.1.1.1. Study design, objectives, locations and dates

This study was a Phase I and Phase III, open label trial. It consisted of 3 parts:

- *Part 1:* included subjects aged at least 18 years with severe haemophilia A. All subjects received a single IV dose of 50 IU/kg of Advate followed by a single IV dose of 50 IU/kg of rVIII-SingleChain (after a wash-out period of 4 days) to enable a comparison of the PK of the 2 products. It was planned to include 30 subjects in Part 1, to ensure a minimum of 26 subjects were evaluable for the PK comparison.
- *Part 2:* subjects enrolled in Part 1 were continued on open-label treatment with rVIII-SingleChain. The first 5 subjects were to receive on demand treatment. The remaining subjects could be treated with either on demand or prophylaxis treatment. This part of the study assessed efficacy and safety in these subjects.
- *Part 3:* enrolled additional subjects with severe haemophilia A (aged ≥ 12 to 65 years). Subjects were treated with open-label treatment with rVIII-SingleChain, either as on demand treatment or prophylaxis for at least 50 exposure days (EDs), with assessment of efficacy and safety. It was planned to enrol approximately 100 subjects in this Part. A subgroup of subjects in Part 3 were also to undergo PK assessment at baseline (following a single dose of 50 IU/kg of rVIII-SingleChain) and again after 3 to 6 months of treatment.

In addition, after enrolment in Part 3 had begun, a surgical sub-study was commenced with a planned enrolment of at least 5 subjects to assess the efficacy and safety of rVIII-SingleChain in the surgical setting. Subjects enrolled in Parts 2 or 3 could participate in the surgical sub-study.

Overall it was planned to enrol at least 104 evaluable subjects in the trial, so that the inhibitor rate could be adequately assessed. Subjects who completed the study could be enrolled in another open extension trial (Study 3001).

The primary objectives of the study were to:

- Characterise the rate of inhibitor formation;
- Characterise the PK profile of rVIII-SingleChain;
- Demonstrate efficacy in the prevention and treatment of bleeding events;
- Demonstrate the efficacy of routine prophylaxis treatment over on demand treatment;

- Demonstrate the efficacy of rVIII-SingleChain in surgical prophylaxis.

The secondary objectives of the study were to:

- Characterise the safety profile of rVIII-SingleChain;
- Perform a PK comparison of rVIII-SingleChain to Advate.

The study was conducted at 54 centres in 20 countries: Australia (2 centres), Austria (2), Canada (1), Czech Republic (1), Germany (6), Hungary (1), Italy (4), Japan (8), Lebanon (1), Malaysia (1), Netherlands (1), Philippines (2), Poland (3), Romania (1), Russian Federation (2), South Africa (2), Spain (3), Ukraine (3), United Kingdom (1) and the United States (9).

The trial commenced in February 2012 and was completed in December 2014. The study report was dated 7 May 2015. The study does not appear to have been published.

7.1.1.2. Inclusion and exclusion criteria

The trial enrolled male subjects with severe haemophilia A, aged ≥ 18 years (Parts 1 and 2) or ≥ 12 to 65 years (Part 3). Only previously treated patients (PTPs), with a previous exposure of > 150 EDs to FVIII products, were enrolled. Subjects with a history or family history of inhibitors were excluded.

Comment: The entry criteria were consistent with those recommended in the EMA guideline.

7.1.1.3. Study treatments

In Part 1, all subjects received a single IV dose of 50 IU/kg of Advate followed by a single IV dose of 50 IU/kg of rVIII-SingleChain (after a wash out period of 4 days).

In Parts 2 and 3, on demand treatment was administered with a dosage regimen similar to that previously used by the subject with his/her prior FVIII product. For prophylaxis, rVIII-SingleChain was administered at a dose of 20 to 40 IU/kg every second day, or 20 to 50 IU/kg 2 to 3 times per week, or at other doses and frequencies at the investigator's discretion. For use during surgery, the dose was individualized based on the type of surgery, any previously obtained PK data for the patient and FVIII levels recommended by the WFH guidelines.[2]

Treatment with on demand or prophylaxis treatment was to be continued for at least 50 EDs.

7.1.1.4. Efficacy variables and outcomes

Efficacy endpoints were designed to assess efficacy for 3 'indications': treatment of bleeding episodes, prophylactic treatment and use in surgery.

For treatment of bleeding episodes and prophylactic use subjects (or their caregivers) recorded the following information in an electronic diary (eDiary): reason for use, location of bleeding, time of the start of bleeding, dose (total IUs), number and lot number of vials used, stop and start times of injection, number of injections required to treat the bleeding. Subjects were reviewed in the clinic at monthly intervals for the first 6 months, and then at 3 monthly intervals.

Treatment of bleeding episodes

The primary efficacy endpoint was the rate of treatment success for bleeding episodes defined as a rating of 'excellent' or 'good' on the investigator's overall clinical assessment of haemostatic efficacy 4 point scale.

Other efficacy endpoints were:

- Number of injections of rVIII-SingleChain required to achieve haemostasis;
- Rate of treatment success for major bleeding episodes (for example, central nervous system, gastrointestinal tract, neck/throat, or severe trauma-induced bleeding). A separate 4 point

efficacy scale was to be used for assessment of efficacy in such bleeds. However, no major bleeding episodes occurred during the study.

Prophylactic treatment

The primary efficacy endpoint was the annualized spontaneous bleeding rate (AsBR, based on the number of spontaneous bleeding episodes).

Other efficacy endpoints were:

- Annualised bleeding rate (ABR, based on the number of all bleeding episodes);
- A comparison of AsBR and ABR between rVIII-SingleChain and Biostate (a plasma derived FVIII product) using historical data for the Biostate product;
- Consumption of rVIII-SingleChain.

Use in surgery

The primary efficacy endpoint was the rate of treatment success defined as an investigator rating of 'excellent' or 'good' on the 4 point efficacy evaluation of surgical treatment scale.

Other efficacy endpoints were:

- Consumption of rVIII-SingleChain during surgical prophylaxis;
- Predicted and estimated blood loss during surgery;
- Predicted and actual transfusion requirements during surgery;
- Change in haemoglobin levels between baseline, intra-operation and post-operation.

Comment: The efficacy endpoints were standard for haemophilia studies and consistent with the recommendations of the EMA guideline.

7.1.1.5. Randomisation and blinding methods

There was no randomisation or blinding used in the study.

7.1.1.6. Analysis populations

The following analysis populations were defined in the protocol:

- The safety population consisted of all subjects who received at least one dose of study medication (Advate or rVIII-SingleChain) during the study.
- The PK population was comprised of subjects who received at least one dose of 50 IU/kg of rVIII-SingleChain and for whom a sufficient number of analysable PK samples were obtained to permit evaluation of the PK profile. Subjects could not have received another FVIII product for the treatment of a bleed during the PK sampling period.
- The efficacy population consisted of all subjects who participated in the non-surgical efficacy portion of the study and received at least one dose of rVIII-SingleChain.
- The Per Protocol (PP) population included all subjects in the efficacy population who completed the study without any major protocol deviations that would impact the assessment of the primary efficacy endpoint. Subjects must have had compliance with no less than 80%, and no more than 120%, of prescribed doses and actual doses within ± 10% of the prescribed dose.
- The surgical population included all subjects enrolled in the surgical substudy who had received at least one dose of rVIII-SingleChain during the surgical substudy.

7.1.1.7. Sample size

For Part 1, it was calculated that a sample size of 26, in a single-sequence crossover design, would have 80% power to reject (using 2, 1-sided tests) both: a) the null hypothesis that the ratio of the test mean to the standard mean in the original scale is below 0.800 and b) the null hypothesis that the ratio of test mean to the standard mean in the original scale is above 1.200; (that is, that the test and standard are not equivalent), in favour of the alternative hypothesis that the means of the 2 groups are equivalent. The sample size estimate also included the assumptions that the expected ratio of means is 1.000, the between-subject coefficient of variation in the original scale is 0.300, the intra-subject coefficient of variation in the original scale is 0.300, and that each one-sided test is made at the 2.5% level of significance.

For the entire study, it was planned to ensure that a total of at least 104 subjects were enrolled and treated with rVIII-SingleChain. Based on a FDA guideline, an upper bound of 6.8% for the 95% CI for the rate of inhibitor development was considered to be acceptable. If 2 or less subjects (out of a total of 104 subjects) developed an inhibitor, the upper bound of the 95% CI would be ≤ 6.8%.

7.1.1.8. Statistical methods

For the primary efficacy endpoint for the treatment of bleeding episodes, the rate of treatment success was calculated together with a 95% CI. Treatment would be considered successful if the lower limit of the 95% CI was above 70%.

The AsBR was compared between subjects managed with on demand treatment and those managed with prophylaxis treatment. The difference between treatments was tested using Poisson regression. Similar analyses were to be conducted for the secondary endpoint of ABR.

For the surgical substudy, the rate of treatment success was calculated: an observed success rate of 70% or greater for excellent or good would be considered acceptable.

A hierarchical approach was used to account for multiplicity of testing:

- If the 95% CI upper bound for the risk of inhibitor development was greater than 6.8%, then the study would have failed and further testing would stop;
- If a risk of inhibitor development of > 6.8% was excluded, efficacy in the treatment of bleeding episodes would be tested. If the lower limit of the 95% CI for the observed success rate was less than 70%, then the study would have failed on this endpoint and further testing would stop.
- If the success rate for the treatment of bleeding episodes was deemed acceptable, a test of the null hypothesis of no difference between the prophylaxis and the on demand groups would be conducted. If the null hypothesis was not rejected at the 2-sided 0.05 level, then the study would have failed on this endpoint and further testing would stop.

Descriptive statistics were used for the analysis of most of the other efficacy outcomes.

7.1.1.9. Participant flow

A total of 175 subjects were enrolled in the study and 174 received treatment. 27 subjects received treatment in Parts 1 and 2 and 147 received treatment in Part 3. A total of 161 subjects completed the study.

The safety population consisted of all 174 subjects who were treated. One subject received rVIII-SingleChain in Part 1 (PK evaluation) but withdrew prior to Part 2 (efficacy and safety evaluation) and hence was not included in the efficacy population.

7.1.1.10. Major protocol violations/deviations

A total of 17 subjects in the efficacy population were excluded from the per protocol population. All were excluded due to lack of compliance. Dose compliance rate was defined as the

proportion of doses (either prophylaxis and on demand) that were within 10% of the prescribed dose. A subject was regarded as compliant with the dose if the dose compliance rate was between 80 and 100%. A subject was regarded as compliant with the prophylaxis schedule if prophylaxis compliance was between 80 and 120%.

7.1.1.11. Baseline data

All subjects were male. The mean age was 31.3 (± 11.77) years. A total of 14 subjects (8.0%) were aged between 12 and 17 years. 72.4% of subjects were White and 17.8% Asian.

Haemophilic arthropathy was reported by 52.3% of subjects, hepatitis C infection by 34.4%, HIV infection by 10.3% and hepatitis B by 5.7%. The most commonly reported surgical procedure was knee arthroplasty (13.2% of subjects).

The median number of spontaneous bleeding episodes in the previous 12 months was 9.0 (range 0 to 168). The median number of traumatic bleeding episodes was 1.0 (range (0 to 66). Genetic testing results were available for 36 of the 174 subjects (20.7%). Among these the most common abnormality was intron 22 inversion (18 subjects).

Approximately half the population had been treated with plasma derived FVIII products and half with recombinant FVIII products. 49.4% had been previously treated with a prophylaxis regimen and 52.9% with an on demand regimen.

7.1.1.12. Results for the primary efficacy outcomes

Treatment of bleeding episodes

Overall there were a total of 848 bleeding episodes in the study that were treated. The rate of treatment success was 92.3% (95% CI: 88.9 to 94.8%). As the lower limit of the 95% CI was > 70%, efficacy in the treatment of bleeding episodes was determined to be acceptable.

Two sensitivity analyses (using different methods of dealing with missing data) gave similar results. The success rate in the per-protocol population was 92.8% (95% CI: 88.8 to 95.4%).

Subgroup analyses were presented for age groups (12 to 17 and 18+years) and geographical location (USA versus Japan versus Europe versus Rest of World). Results obtained for these subgroups were similar to the primary analysis.

Prophylactic treatment

The annualised spontaneous bleeding rate (AsBR) was 19.5 (95% CI: 17.8 to 21-3) spontaneous bleeds per year in the on-demand treatment group and 1.6 (95% CI: 1.3 to 1.8) spontaneous bleeds per year in the prophylactic treatment group. The AsBR was reduced by 92% (ratio = 0.08; 95% CI: 0.09 to 0.10). The difference between treatment groups was statistically significant ($p < 0.0001$). Similar results were observed in the per protocol population.

Use in surgery

A total of 13 subjects underwent a total of 16 procedures in the surgical substudy. The overall clinical assessment of efficacy was 'excellent' in 15 procedures (93.8%) and 'good' in 1 procedure (6.3%). Overall success rate was therefore 100%.

Comment: The EMA guideline requires that efficacy in the surgical setting be studied in a minimum of 5 patients undergoing at least 10 major surgical procedures. The sponsor defined a major surgery as a surgical procedure that involved anaesthesia (general, spinal, epidural or regional block) or respiratory assistance (including but not limited to orthopaedic and cardiac surgery). All 16 surgeries were classed as major by the sponsor. Although some of the procedures might reasonably be considered as minor (for example, circumcision, and wisdom teeth extraction), the minimum requirement of 10 major procedures has been met.

7.1.1.13. Results for other efficacy outcomes

Treatment of bleeding episodes

Number of injections of rVIII-SingleChain required to achieve haemostasis: In 92.5% of episodes, haemostasis was achieved with 1 or 2 injections.

Rate of treatment success for major bleeding episodes: No major bleeding episodes occurred in the study.

Prophylactic treatment

Annualised bleeding rate (ABR): The ABR (based on all bleeding episodes) was 24.9 (95% CI: 23.0 to 27.0) bleeds per year in the on demand treatment group and 2.6 (95% CI: 2.3 to 2.9) bleeds per year in the prophylactic treatment group. The ABR was reduced by 90% (ratio = 0.10; 95% CI: 0.09 to 0.12). The difference between treatment groups was statistically significant ($p < 0.0001$).

A subgroup analysis of ABR by geographical region was performed. Prophylactic treatment was associated with a statistically significant ($p < 0.0001$) reduction in ABR compared to on demand treatment for all regions except Japan. In Japan, there were only 9 subjects in the prophylactic treatment group and 1 subject in the on demand treatment group, and the difference in ABR did not reach statistical significance ($p = 0.0845$).

Comparison of AsBR/ABR with historical control (Biostate): In the historical study, Biostate was used for on-demand treatment and limited preventative therapy (administering study drug as a precautionary measure prior to physical exercise) in 52 subjects. Prophylaxis with rVIII-SingleChain was associated with a significantly reduced AsBR and ABR when compared to on demand/preventative use of Biostate.

Consumption of rVIII-SingleChain: Most subjects were assigned to a thrice-weekly regimen (n = 79, median dose 30.0 IU/kg) or twice weekly regimen (n = 46, median dose 35.0 IU/kg). Most of these subjects did not require dose adjustment during the study. Only one subject required dosing at > 50 IU/kg per dose.

Use in surgery

Consumption of rVIII-SingleChain during surgical prophylaxis: Total rVIII-SingleChain consumption ranged from 129.11 IU/kg (for removal of internal fixation from an ankle) to 1725.19 IU/kg (for revision of a knee prosthesis).

Predicted and estimated blood loss during surgery: Mean observed intraoperative blood loss was 73.3 (± 107.18) mL. This was lower than the mean predicted value (259.3 ± 369.42 mL).

Predicted and actual transfusion requirements during surgery: The mean (± SD) actual volume of packed red blood cells transfused was 0.7 (± 1.78) mL. This was slightly less than the mean predicted volume of 1.1 (± 1.78) mL. There were no other blood products transfused.

Change in haemoglobin levels between baseline, intra-operation and post-operation: There was a small reduction in average haemoglobin levels in the post-operative period.

7.1.2. Study 3002

7.1.2.1. Study design, objectives, locations and dates

The study was a Phase III, open-label trial in previously-treated paediatric subjects (aged < 12 years) with severe haemophilia A. The study included a pharmacokinetic period in which a subgroup of subjects received a single dose of 50 IU/kg of rVIII-SingleChain at Baseline. All subjects were then enrolled in a treatment period during which rVIII-SingleChain was administered either as on demand or prophylactic therapy for at least 50 EDs.

The primary objective was to evaluate the efficacy of rVIII-SingleChain in the treatment of bleeding episodes based on an investigator's 4 point assessment scale.

The secondary objectives of the study were to:

- Evaluate the annualised bleeding rate (ABR) during prophylaxis treatment;
- Evaluate the ABR during on demand treatment;
- Evaluate the proportion of bleeding episodes requiring 1, 2, 3, or > 3 injections of rVIII-SingleChain to achieve haemostasis;
- Evaluate the consumption of rVIII-SingleChain;
- Evaluate the PK profile of rVIII-SingleChain;
- Assess the rate of inhibitor formation to rVIII-SingleChain;
- Assess the safety of rVIII-SingleChain.

The study was conducted at 37 centres in 19 countries: Australia (1 centre), Austria (2), France (5), Georgia (1), Germany (4), Italy (1), Lebanon (1), Malaysia (1), Netherlands (3), Philippines (2), Poland (1), Portugal (1), Romania (1), Spain (1), Switzerland (1), Thailand (5), Turkey (3), Ukraine (1) and the United States (2).

The study commenced in March 2014 and was completed in August 2015. The submitted study report was dated 25 November 2015. The study does not appear to have been published.

7.1.2.2. Inclusion and exclusion criteria

The trial enrolled male subjects with severe haemophilia A, aged < 12 years. Only previously-treated patients (PTPs), with a previous exposure of > 50 EDs to FVIII products, were enrolled. Subjects with a history or first order family history of inhibitors were excluded.

Comment: The entry criteria were again consistent with the recommendations of the EMA guideline.

7.1.2.3. Study treatments

In the PK period, a subgroup of subjects received a single dose of 50 IU/kg of rVIII-SingleChain on Day 1.

In the treatment period subjects were treated with rVIII-SingleChain as either on demand or prophylactic therapy.

- The dose used for the treatment of a bleeding episode was determined by the investigator, based on previous FVIII dose, any available PK data and the subject's bleeding phenotype. The target FVIII activity level was based on WFH guidelines.[2]
- For prophylactic therapy, subjects received rVIII-SingleChain at a dose of 15 to 50 IU/kg every second day, or 2 to 3 times per week, or at a dose and frequency determined by the investigator based on previous FVIII dosing and available PK data.

Treatment was continued until 50 EDs had been reached. This was expected to take approximately 6 months for subjects on prophylactic therapy and up to 2 years for subjects receiving on demand therapy.

Treatment with rVIII-SingleChain during major surgery was not permitted and subjects were to be withdrawn from the study if major surgery could not be avoided.

7.1.2.4. Efficacy variables and outcomes

The main efficacy variables were:

- The investigator's subjective assessment of efficacy in the treatment of bleeding episodes;

- Annualised bleeding rates;
- The number of rVIII-SingleChain injections required to achieve haemostasis in the control of bleeding episodes;
- Consumption of rVIII-SingleChain.

For treatment of bleeding episodes and prophylactic use subjects (or their caregivers) recorded the following information in an electronic diary (eDiary): reason for use, location of bleeding, time of the start of bleeding, dose (total IUs), number and lot number of vials used, stop and start times of injection, number of injections required to treat the bleeding. Subjects were reviewed in the clinic at monthly intervals for the first 6 months, and then at 3 monthly intervals.

The primary endpoint of the study was treatment success, defined as a rating of 'excellent' or 'good' on the investigator's overall clinical assessment of haemostatic efficacy, for all treated bleeding events (major or minor). The investigator's overall assessment consisted of a 4 point scale (excellent, good, moderate and poor/none).

Comment: In Study 1001 definitions of 'excellent', 'good' and so on were provided. No definitions were provided in the protocol or report for Study 3002. The sponsor should be asked to clarify whether any definitions were used for these ratings.

Secondary efficacy endpoints were:

- Annualised rate of bleeding (traumatic and non-traumatic/spontaneous) during on-demand therapy and during prophylaxis treatment;
- Occurrence of bleeding (traumatic or non-traumatic/spontaneous) requiring 1, 2, 3, or > 3 injections of rVIII-SingleChain to achieve haemostasis;
- Consumption of rVIII-SingleChain, expressed as number of injections and International units (IU)/kg per month and per year, as well as IU/kg per event for both on-demand and prophylaxis treatment.

Comment: The efficacy endpoints were again consistent with the recommendations of the EMA guideline.

7.1.2.5. Randomisation and blinding methods

There was no randomisation or blinding used in the study.

7.1.2.6. Analysis populations

The safety population: consisted of all subjects who received at least one dose of rVIII-SingleChain during the study.

The PK population: was comprised of subjects who received at least one dose of 50 IU/kg of rVIII-SingleChain and for whom a sufficient number of analysable PK samples were obtained to permit evaluation of the PK profile. Subjects could not have received another FVIII product for the treatment of a bleed during the PK sampling period.

The efficacy population: consisted of all subjects who received at least one dose of rVIII-SingleChain as part of either a routine prophylaxis or on demand regimen during the study.

The Per Protocol (PP) population: included all subjects in the efficacy population who completed the study without any major protocol deviations that would impact the assessment of the primary efficacy endpoint.

7.1.2.7. Sample size

The sample size was based on the EMA guideline for FVIII products which requires at least 50 previously-treated children to be studied. These are to be allocated to 2 age cohorts: a minimum of 25 patients aged of 6 to < 12 years and at least 25 patients aged < 6 years. A total of approximately 75 subjects were planned to be enrolled in the study to ensure that at least 25 subjects in each age group receive 50 EDs of rVIII-SingleChain.

7.1.2.8. Statistical methods

Descriptive statistics were used to summarise the efficacy data. There were no a priori statistical hypotheses or predefined success criteria.

7.1.2.9. Participant flow

A total of 84 subjects were enrolled and treated in the study: 35 in the < 6 years age group and 49 in the ≥ 6 to < 12 years age group. Only 3 of the 84 subjects were assigned to an on-demand regimen. A total of 65 subjects completed the study, 27 in the < 6 years age group and 38 in the ≥ 6 to < 12 years age group. Most of the subjects who discontinued the study were terminated by the sponsor after the required minimum 25 patients in each age group had completed 50 EDs.

7.1.2.10. Major protocol violations/deviations

One subject was excluded from the efficacy population. This subject was identified as having a pre-existing inhibitor to FVIII, based on re-examination of the screening blood sample that had initially been reported as negative due to laboratory process error. Although excluded from the efficacy population the subject continued in the study.

Eight subjects in the efficacy population were excluded from the per protocol population due to non-compliance with the prescribed dose and/or regimen.

7.1.2.11. Baseline data

All subjects were male. Median age was 7.0 years (range 1.0 to 11.0). 61 subjects were White, 22 were Asian and 1 was 'other'.

Eleven subjects (13.1%) gave a history of haemophilic arthropathy. No subjects had a history of HIV, hepatitis B or hepatitis C infection.

No analysis was provided for previous history of bleeds. Genetic testing results were available for 36 of the 84 subjects (46.4%). Among these the most common abnormality was intron 22 inversion (14 subjects).

Prior to enrolment, 58.3% of subjects were using a recombinant FVIII product and 39.3% were using a plasma-derived product. 71.4% of subjects were on a prophylaxis regimen.

7.1.2.12. Results for the primary efficacy outcome

Overall there were a total of 347 bleeding episodes in the study that were treated (50 in subjects aged < 6 years and 297 in subjects aged ≥ 6 to < 12 years). The rate of treatment success was 96.3% (95% CI: 91.3 to 98.4%).

Two sensitivity analyses (using different methods of dealing with missing data) gave identical results. In the per protocol population the success rate was 97.8% (95% CI: 95.0 to 99.1%).

Subgroup analysis by age group demonstrated that the success rate was 94.0% (95% CI: 83.7 to 97.9) for subjects aged < 6 years and 96.6% (95% CI: 90.6 to 98.8) for subjects aged ≥ 6 to < 12 years. Other subgroup analyses by race (White, race, other) and geographical region (USA, Europe, rest of world) all demonstrated mean success rates of ≥ 90% in all subgroups.

7.1.2.13. Results for other efficacy outcomes

Number of injections of rVIII-SingleChain to achieve haemostasis: In 95.7% of episodes, haemostasis was achieved with 1 or 2 injections. For subjects aged < 6 years the figure was 94.0% and for subjects aged ≥ 6 to < 12 years it was 95.9%.

Consumption of rVIII-SingleChain:

- For subjects allocated to on-demand treatment (n = 3) the mean initial dose assigned was 26.0 IU/kg. The mean final assigned dose was 25.0 IU/kg.
- For subjects allocated to prophylactic treatment (n = 80), the most commonly used regimens were thrice weekly (n = 24) or twice weekly (n = 43). There were only slight differences between mean initial and mean final doses. Approximately 60% of subjects did not require dose adjustment during the study.

Consumption of rVIII-SingleChain during on-demand treatment (n = 3) was, as expected, greater with prophylaxis therapy (n = 80).

During prophylaxis, mean monthly consumption of rVIII-SingleChain was comparable in the 2 age subgroups: 369 (± 125.7) IU/kg per month in the < 6 years group and 352 (± 123.9) IU/kg per month in the ≥ 6 to < 12 years group.

Annualised rate of bleeding: The annualised *spontaneous* bleeding rate (AsBR) was 28.7 (95% CI: 21.9 to 37.6) spontaneous bleeds per year in the on demand treatment group and 1.9 (95% CI: 1.5 to 2.4) spontaneous bleeds per year in the prophylactic treatment group.

For subjects aged < 6 years receiving prophylaxis the AsBR was 0.9 (95% CI: 0.5 to 1.5) and for subjects aged ≥ 6 to < 12 years it was 2.6 (95% CI: 2.0 to 3.3).

Among subjects receiving prophylaxis regimens with an initial assigned dose between 15 and 50 IU per dose (n = 74) the AsBR was similar between the different regimens (3.6 for every second day regimens, 1.8 for thrice weekly regimens, 1.9 for twice weekly regimens and 2.5 for other regimens).

The annualised *total* bleeding rate (ABR) was 71.5 (95%CI: 60.3 to 84.8) bleeds per year in the on demand treatment group and 5.5 (95%CI: 4.8 to 6.3) bleeds per year in the prophylactic treatment group.

For subjects aged < 6 years receiving prophylaxis the ABR was 3.0 (95%CI: 2.3 to 4.0) and for subjects aged ≥ 6 to < 12 years it was 7.4 (95%CI: 6.3 to 8.6).

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

There were no pooled analyses or meta-analyses of efficacy data included in the submission.

7.3. Evaluator's conclusions on clinical efficacy

The pivotal studies complied with the requirements of the EMA guideline for Factor VIII products. The guideline states that pharmacokinetic endpoints such as incremental recovery, half-life, AUC and clearance are important surrogate endpoints for efficacy for a FVIII product. As described in section 4 of this report, the PK data for rVIII-SingleChain indicate that the product restores FVIII activity to plasma of subjects with severe FVIII deficiency, with a half-life that is comparable to other FVIII products.

As recommended by the EMA guideline, the 2 pivotal studies were conducted in previously treated patients (PTPs).

Study 1001: examined efficacy in adults and adolescents. This study demonstrated that the efficacy of rVIII-SingleChain in treating bleeding episodes was assessed as 'excellent' or 'good' in 92.3% of instances. In 92.5% of bleeding episodes, haemostasis was achieved with 1 or 2 injections.

When used as prophylactic therapy, rVIII-SingleChain was associated with a low rate of spontaneous bleeds (1.6 per year), which was significantly lower than the rate observed in subjects receiving on demand therapy (19.5 per year). A similar reduction was observed for the rate of total bleeds per year.

Study 3002: examined efficacy in paediatric subjects aged < 12 years. In this study the efficacy of rVIII-SingleChain in treating bleeding episodes was assessed as 'excellent' or 'good' in 96.3% of instances. In 95.7% of episodes, haemostasis was achieved with 1 or 2 injections.

Prophylaxis with rVIII-SingleChain was associated with a low rate of spontaneous bleeding (1.9 per year), which was lower than the rate observed in subjects receiving on demand therapy (28.7 per year). A similar reduction was observed for the rate of total bleeds per year.

These data indicate that rVIII-SingleChain is effective for prophylaxis therapy and the treatment of bleeding episodes in previously treated patients.

Efficacy in surgery: was assessed in a total of 16 surgeries in 13 subjects. The investigators assessed haemostasis as 'excellent' or 'good' in all cases.

The dosage regimens proposed by the sponsor are appropriate. The recommended dose for prophylaxis in the draft PI is 20 to 50 IU/kg given 2 or 3 times a week. Twice per week and 3 times per week regimens were the most common prophylaxis regimens used in the pivotal studies. Prophylaxis regimens have traditionally aimed to maintain a factor VIII activity level of > 1% at trough. Bleeding episodes are observed infrequently in subjects who are able to maintain such levels.[8] The population PK analysis suggested that the lowest proposed dose (20 IU/kg twice a week) would result in FVIII activity levels of > 1% at trough in 54% of subjects. Therefore, some patients will require higher doses. Each patient will require titration to an appropriate prophylactic dose, as is the case with other FVIII products.

The PK data indicate that rVIII-SingleChain restores factor VIII activity levels to a similar degree as other FVIII products. The dosing regimens proposed by the sponsor for the treatment of haemorrhage, for prophylaxis and for use in surgery are similar to those approved for other FVIII products (with the exception of Eloctate, which is a long acting FVIII product).

No specific dose amendments are proposed for paediatric use, although children had an increased clearance compared with adults. However, the PI contains a statement that higher doses or more frequent dosing may be required in children. This approach is similar to that taken for other FVIII products registered in Australia.

Efficacy has not been studied in previously untreated patients (PUPs) or in subjects with inhibitors. Studies in these populations are not required prior to registration according to the EMA guideline adopted by the TGA.

Overall the efficacy data are considered adequate to support registration of the product.

[8] Jiménez-Yuste V, et al. Achieving and maintaining an optimal trough level for prophylaxis in haemophilia: the past, the present and the future. Blood Transfus; 2014; 12: 314-9.

8. Clinical safety

8.1. Studies providing evaluable safety data

Safety data were collected in the 2 pivotal studies. In addition, the sponsor provided safety data from Study 3001, an open long term extension study for subjects who had completed one of the pivotal studies. This study enrolled a total of 154 subjects (132 subjects from Study 1001 and 22 subjects from Study 3002).

In the 3 studies, the following safety data were collected:

- General adverse events (AEs) were assessed on an ongoing basis throughout the studies. At each visit, investigators specifically inquired (via non-leading questioning) about any AEs that might have occurred since the last visit. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA).
- AEs of special interest (AESIs) were thromboembolic events, hypersensitivity and anaphylactic reactions. Such events were analysed using standardised MedDRA queries (SMQs).
- Physical examination and measurement of vital signs were performed at each clinic visit;
- Local tolerability of injections was assessed by subjects using a 5-point scale (0 =none to 4 = severe). The rating was recorded in the eDiary approximately 30 minutes after each injection. For injections administered in the clinic the investigator assessed local tolerability using a 5 point scale for each of the following 3 signs: erythema, oedema or induration and itching, local pain or heat.

The following immunogenicity related data were collected:

Inhibitors against FVIII: Anti-FVIII neutralising antibodies were quantified using the Bethesda assay with the Nijmegen modification. Results were expressed as Bethesda units (BU) per mL. A positive assay was defined as ≥ 0.6 BU/mL.

Antibodies against rVIII-SingleChain (non-neutralising antidrug antibodies): A screening assay (direct binding ELISA) was used to detect antibodies against the rVIII-SingleChain molecule in blood samples. If this assay was positive, the samples were tested with 2 confirmatory direct-binding ELISA assays.

Antibodies against CHO host cell protein: An ELISA screening assay was performed. In the event of a positive assay confirmatory assays were performed.

These tests were performed at a central laboratory. They were performed at screening and at monthly intervals in Study 1001. In Study 3002 they were performed at screening, after 10 to 15 EDs and after 50 to 75 EDs. In Study 3001, they were collected after 10, 50 and 100 EDs.

Other laboratory tests, including the following, were performed:

Biochemistry: Sodium, potassium, chloride, blood urea nitrogen, creatinine, gamma-glutamyl transferase, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, albumin, total bilirubin, total protein, glucose, calcium, urea and lactate dehydrogenase.

Haematology: Haemoglobin, haematocrit, mean corpuscular volume (MCV), erythrocyte count, leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, and basophils and platelets.

These were performed at screening and at each study visit in the pivotal studies and every 3 months in Study 3001.

8.2. Patient exposure

A total of 258 subjects were treated with rVIII-SingleChain in the submitted studies. The median number of exposure days was 63.5 in Study 1001 and 58.5 in Study 3002. For those subjects who continued into Study 3001, the median total exposure was 135.5 days.

Mean study duration was 8.5 months for Study 1001, 6.0 months for Study 3002 and 5.3 months for Study 3001.

Comment: The extent of patient exposure meets the requirements of the EMA guideline for a new FVIII product.

8.3. Adverse events

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

8.3.1.1. Pivotal studies

In Study 1001, the overall incidence of AEs was 64.9%.

In Study 3002, the overall incidence of AEs was 76.2%.

8.3.1.2. Study 3001

In Study 3001 the average duration of follow-up was shorter than in the pivotal studies. The overall incidence of AEs was 31.2%.

Comment: The common AEs were non-specific events which might be expected in a cohort of haemophilia A patients followed for several months. Most of the AEs were rated as mild, with only a small proportion of patients experiencing severe AEs.

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

8.3.2.1. Pivotal studies

In Study 1001, the overall incidence of treatment-related AEs was 7.5%. The only treatment related events that occurred in more than one subject were dizziness and hypersensitivity (n = 2 for both). All events were rated as mild or moderate except for one event of severe hypersensitivity.

In Study 3002, the overall incidence of treatment-related AEs was 1.2%. (that is, 1 of 84 subjects). This subject experienced one mild hypersensitivity event.

8.3.2.2. Study 3001

In Study 3001, the overall incidence of treatment-related AEs was 0.6%. (that is, 1 of 154 subjects). This subject experienced one event of drug hypersensitivity which was rated as moderate.

8.3.3. Deaths and other serious adverse events

8.3.3.1. Deaths

There were no deaths in the submitted studies.

8.3.3.2. Non-fatal serious AEs

Pivotal studies

In Study 1001, the overall incidence of serious AEs was 4.0%. Only one of these events (hypersensitivity) was assessed as being related to rVIII-SingleChain.

In Study 3002, the overall incidence of serious AEs was 10.7%. None of these events were assessed as being related to rVIII-SingleChain.

Study 3001

In Study 3001, the overall incidence of serious AEs was 3.2%. Again, none of these events were assessed as being related to rVIII-SingleChain.

8.3.4. Discontinuation due to adverse events

8.3.4.1. Pivotal studies

In Study 1001, there were no discontinuations due to AEs.

In Study 3002, 1 subject (1.2%) withdrew due to moderate hip arthralgia. The event was assessed as being not related to rVIII-SingleChain.

8.3.4.2. Study 3001

In Study 3001, there were 2 discontinuations due to AEs (1.3%). 1 subject withdrew due drug hypersensitivity which was assessed as related to rVIII-SingleChain. The other withdrawal was due to nephritis, which was assessed as unrelated to the study drug.

8.3.5. AEs of special interest

8.3.5.1. Thromboembolic events

There were no thromboembolic events observed in the 3 submitted studies. One subject in Study 3002 developed an event of 'device occlusion' which was considered unrelated to the study drug.

8.3.5.2. Hypersensitivity/Anaphylaxis

There were no reports of the specific term 'anaphylaxis' in the 3 submitted studies.

In the 3 studies there were a total of 4 reported events of 'hypersensitivity' or 'drug hypersensitivity':

- A 17 year old male in Study 1001 who was receiving a prophylaxis regimen developed severe hypersensitivity (pruritus, fever, erythema, headache, dyspnoea, chest discomfort, and rash) approximately 2.5 hours after an injection. He was treated in hospital with steroids and an antihistamine and the event resolved after approximately 17.5 hours. The subject continued in the study with antihistamine premedication and had no further hypersensitivity events. The event was assessed as serious and related to rVIII-SingleChain.
- A 32 year old male in Study 1001 experienced 2 mild hypersensitivity events (details not provided) 3 days apart. He was continued in the study with antihistamine premedication and no further events were reported. The events were assessed as non-serious but related to the study drug.
- A 9 year old boy in Study 3002 experienced a mild hypersensitivity event (details not provided) 2 days after his first injection. He was treated with antihistamines and the event resolved on the same day. He was continued in the study and no further events were reported. The event was assessed as non-serious but related to the study drug.
- A 55 year old male in study in Study 3001, who was receiving a prophylaxis regimen, developed an event of moderate drug hypersensitivity (details not provided) after 65 EDs. A re-challenge (without premedication) was positive and the subject was withdrawn from the study. The event was assessed as non-serious but related to the study drug.

8.3.5.3. Local tolerability

For results for subject assessment of local tolerability and investigator assessment of erythema in Study 1001, according to the subjects, 99.3% of injections were associated with no local reaction. According to the investigator 99.8% of injections were associated with no erythema. There were no investigator observations of oedema/induration or itching/local pain/heat.

Similar results were observed in the other 2 studies.

8.3.5.4. AEs during surgery

None of the AEs that commenced during the surgical period of Study 1001 were assessed as being related to rVIII-SingleChain.

Four subjects in Study 3001 had undergone surgical procedures. One subject had an AE of 'bone pseudocyst'. However, this event appears to have occurred before the surgical procedure (which was an excision and bone grafting of a pseudotumour in the radius and ulna). The event was assessed as being unrelated to study drug.

8.4. Laboratory tests

8.4.1. Inhibitor development

No subjects developed FVIII inhibitors in any of the 3 studies.

One subject in Study 3002 was noted to have a low-titre inhibitor (0.90 BU/mL) at the 1 month visit. However, re-testing of the sample collected at screening demonstrated a pre-existing low titre inhibitor (3.46 BU/mL). Due to a laboratory process error, the screening sample had initially been reported as negative.

Characterisation of the rate of inhibitor formation was one of the primary objectives of Study 1001.

For calculating the incidence rate, the numerator included all subjects with inhibitors regardless of EDs to rVIII-SingleChain, and the denominator included subjects with at least 50 EDs plus subjects with less than 50 EDs but with an inhibitor. A 2 sided 95% CI was calculated. An acceptable rate of inhibitor formation would be concluded if the upper confidence limit was less than 6.8%.

There were no subjects with inhibitors and 120 subjects with at least 50 EDs. The calculated rate of inhibitor formation was 0% (95% CI: 0 to 3.0%). As the upper 95% CI was < 6.8%, the rate of inhibitor formation was considered acceptable.

8.4.2. Antibodies against rVIII-SingleChain (non-neutralising anti-drug antibodies)

In all 3 studies there were a proportion of subjects who were positive for such antibodies at Baseline.

The incidence of subjects who were negative at Baseline and became positive after Baseline was 2.3% in Study 1001, 11.9% in Study 3002 and 0% in Study 3001.

The development of ADAs was not associated with any apparent increased risk of AEs or loss of efficacy. There were 14 subjects who developed ADAs and had PK data. According to the sponsor the PK profiles in these subjects were similar to those in subjects without ADAs.

8.4.3. Antibodies against CHO host cell protein

No subjects developed antibodies against CHO cell proteins.

8.4.4. Other laboratory tests

The study report presented limited analyses of other laboratory testing data. The results of haematology and biochemistry tests in Studies 1001 and 3002 were mainly presented as line listings over several thousand pages. Some abnormal laboratory results were identified as being 'clinically significant', although the criteria used to assign results to this category were not clear. It was not possible to determine the overall incidence of specific laboratory abnormalities.

Scanning of the line listings for events determined to be clinically significant suggested that such abnormalities were sporadic and infrequent. Abnormal LFTs were observed in subjects with pre-existing hepatitis and subjects with abnormal LFTs often had abnormal results at baseline.

Any value outside the reference range and considered to be clinically significant by the investigator at any visit after the first injection of rVIII-SingleChain was supposed to be recorded as a treatment emergent adverse event (TEAE). In Study 3002, there was one TEAE of decreased haemoglobin.

No biochemistry or haematology results were presented for Study 3001.

Comment: The presentation of the haematology and biochemistry laboratory test results in the study reports was generally uninformative.

8.4.5. Vital signs

In Study 1001, mean systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate and temperature values were within normal limits throughout the study. One subject had a clinically significant decrease in DBP and another had a clinically significant increase in DBP.

In Study 3002, mean systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate and temperature values were within normal limits throughout the study. There were sporadic incidences of clinically significant changes, but no consistent trends.

Vital signs data were not presented for Study 3001.

8.5. Post-marketing experience

There were no post-marketing data contained in this submission.

8.6. Safety issues with the potential for major regulatory impact

8.6.1. Liver toxicity

There were no serious hepatic adverse events reported in the 3 clinical studies. Analysis of LFT data was very limited. However, most subjects with abnormal LFTs appeared to have abnormal results at baseline and/or were known to have hepatitis.

8.6.2. Haematological toxicity

There was one report of serious anaemia in Study 3002. This was in a 1 year old child who had a central line inserted and presented with recurrent episodes of anaemia requiring transfusion. All investigations for a cause of the anaemia were negative. The cause was eventually attributed to Munchausen syndrome (by proxy). There were no reports of serious haematological events in the other studies.

Analysis of haematology laboratory data was very limited. However, clinically significant abnormalities appeared to be sporadic and infrequent.

8.6.3. Serious skin reactions

There were no serious dermatological adverse events reported in the 3 studies.

8.6.4. Cardiovascular safety

There were no serious cardiac or vascular adverse events reported in the 3 studies.

8.6.5. Unwanted immunological events

The incidence of inhibitors and anti-drug antibodies and hypersensitivity events is discussed in Section 8.4, above.

8.6.6. Other safety issues

8.6.6.1. Safety in special populations

The Summary of Clinical Safety of the submission presented a breakdown of AEs according to age group and shows the overall incidence of AEs, SAEs and so on presented by age group in the 2 pivotal studies. The tabulation suggests that AEs and SAEs were more common in children than in adults. However, AEs assessed as being related to the drug were more common in adolescents and adults.

There were no analyses of safety presented for other subpopulations.

8.7. Evaluator's overall conclusions on clinical safety

The total number of subjects exposed to rVIII-SingleChain in the submitted clinical studies was 258. Of these, a total of 185 subjects received at least 50 exposure days of treatment. This is in excess of the total number of subjects required by the relevant EMA guideline adopted by the TGA (a total of 100 subjects with at least 50 exposure days).

The major safety issue with FVIII products is the development of inhibitors. No cases of inhibitor development were observed in the submitted studies of rVIII-SingleChain. However, only previously treated patients (PTPs) at low risk of inhibitor development were enrolled in the submitted studies. In previously untreated patients (PUPs) with severe haemophilia A, inhibitors form in approximately 30% of subjects, usually during the first 30 exposure days.[3] A recently published randomised trial demonstrated that the incidence of inhibitor development in PUPs is higher with recombinant products than with plasma-derived products.[9] The EMA guideline requires that a study of safety, efficacy and PK in PUPs should be commenced prior to a marketing authorisation of a novel FVIII product, and the sponsor is enrolling PUPs in an additional arm of Study 3001 (Arm 2). The sponsor should be asked to provide a summary of any available data on inhibitor development in these subjects.

The adverse event profile of rVIII-SingleChain observed in the submitted studies was generally consistent with that expected for a FVIII product. Cases of hypersensitivity were observed. However, only one subject discontinued treatment due to a hypersensitivity event. Other cases were able to continue treatment with antihistamine premedication. No cases of anaphylaxis were observed. There were no thromboembolic events reported.

Other AEs observed commonly in the submitted studies were non-specific that might commonly be observed in the general population (nasopharyngitis, arthralgia, headache, rash, cough, pyrexia). The proportion of such events assessed as being related to the drug was low.

Overall the safety profile of rVIII-SingleChain is considered acceptable.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of rVIII-SingleChain in subjects with haemophilia A are:

- Restoration of plasma factor VIII activity;
- A reduction in the incidence of bleeding episodes when a prophylaxis regimen is used;
- Adequate control of bleeding episodes when they occur, usually with 1 or 2 injections only;

[9] Peyvandi F et al. A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A. N Engl J Med. 2016; 374: 2054-64.

- Adequate control of bleeding during surgical procedures.

9.2. First round assessment of risks

The risks of rVIII-SingleChain in subjects with haemophilia B are:

- Hypersensitivity reactions;
- Other minor adverse events (for example, arthralgia, headache, rash, cough, and pyrexia).
- Although no cases of inhibitor development occurred in the submitted studies, it can be expected that such cases will occur.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of rVIII-SingleChain in the treatment of haemophilia A is favourable.

10. First round recommendation regarding authorisation

It is recommended that the application for registration be approved.

11. Clinical questions

11.1. Pharmacokinetics

1. The proposed correction factor for converting one stage assay results to chromogenic assay results is 1.8. It is noted that in the approved prescribing information for the United States, the correction factor is 2.0. Please comment on the reasons for this difference.

11.2. Efficacy

2. In Study 3002, the primary endpoint was the investigator's overall assessment of haemostatic efficacy, which consisted of a 4 point scale (excellent, good, moderate, poor/none). The study report, protocol and SAP did not contain definitions of the terms 'excellent', 'good', and so on. Please clarify whether any definitions were provided to investigators, and if so, please provide a copy.

11.3. Safety

3. Please provide a summary of any available data on inhibitor development and hypersensitivity events in previously untreated patients (PUPs) treated with rVIII-SingleChain in Study 3001 (Arm 2).

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

A second round clinical evaluation report was not completed for this submission, as only 3 targeted clarification questions were posed to the sponsor. These were satisfactorily addressed in the sponsor's responses.

13. References

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