



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research**

MEMORANDUM

Date: 28 February 2014

From: Wambui Chege, MD
Medical Officer, Therapeutics and Blood Safety Branch

Re: STN 125487\0

Through: Christopher Jankosky, MD, MPH
Branch Chief, Therapeutics and Blood Safety Branch

Michael Nguyen, MD
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Product: Eloctate [Antihemophilic Factor (Recombinant Fc Fusion Protein)]

Subject: Original Biologics License Application (Initial Action Due Date 08Mar2014, extended to 07Jun2014 due to Major Amendment)

Sponsor: Biogen Idec

1. INTRODUCTION

1.1 Product Description

1.1.1 Background

On 07 March 2013, Biogen Idec submitted an original Biologics License Application (BLA, 125487\0) to the Food and Drug Administration (FDA) for Eloctate (rFVIII_{IFc}) - a long-acting, recombinant antihemophilic product comprised of a B-domain deleted recombinant human factor VIII (BDDrFVIII) covalently linked to the Fc domain of human immunoglobulin G1 (IgG1). The BDDrFVIII portion of the molecule functions to replace the missing clotting FVIII needed for effective hemostasis in patients with hemophilia A. Fusion to the Fc portion of IgG1 confers a longer half-life to this FVIII product in the following way. The Fc region of human IgG1 binds to neonatal Fc receptor (FcRn). This receptor is expressed throughout life and is part of a pathway that protects Ig from lysosomal degradation by cycling these proteins back into circulation, resulting in a long plasma half-life.¹ Eloctate binds to FcRn, thereby utilizing this same pathway to delay lysosomal degradation, resulting in a longer plasma half-life than endogenous FVIII. Should Eloctate be approved by FDA, it will be the first long-acting FVIII product available on the US market.

The sponsor proposes the following indications for both adults and children ≥ 12 years old with hemophilia A:

- Control and prevention of bleeding episodes
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes
- Perioperative management (surgical prophylaxis)

Eloctate is produced in a human embryonic kidney (HEK) cell line using a cell culture medium that does not contain any proteins derived from animal or human sources. In addition, no human or animal derived additives such as monoclonal antibodies are used in the purification or formulation of the product.

Eloctate will be supplied as a lyophilized powder in single use vials with a prefilled syringe of the diluent, sterile water for intravenous injection. The product will be supplied in seven different strengths - 250, 500, 750, 1000, 1500, 2000 or 3000 International Units (IU) per vial. When reconstituted with sterile water, the product contains the following excipients: sucrose, sodium chloride, L-histidine, calcium chloride, and polysorbate 20.

1.1.2 Long-acting FVIII products – the newest subset of the class

There are currently 11 FVIII products approved by the FDA which are indicated for treatment of hemophilia A. All 11 products are listed in chronological order by date of FDA approval in Table 1 below. If approved by FDA, Eloctate would be the twelfth FVIII product available on the US market and the first long-acting FVIII product available in the US.

¹ Roopenian DC and Akilesh S. FcRn: the neonatal Fc receptor comes of age. *Nat Rev Imm* (2007) 7:715-26

Table 1. Factor VIII Products Approved or Under Review by FDA for Treatment of Hemophilia A

	Product Name	STN	Date of FDA Approval#	Product Details	Product Half Life (h)†		Recommended Dosing Frequency†		
					Adult	Pediatric	Hemorrhage	Surgery	Routine Prophylaxis
1	Hemofil M	101448	11Mar1966	pd	14.8±3		q8-24h	x1, q8-24h	NI
2	Koate-DVI	101130	24Jan1974	pd	16.12		x1, q8-12h	q6-12h	NI
3	Alphanate	102475	15Aug1978	vpd	17.9±10	NR	q12h	q12h	NI
4	Recombinate	103375	10Dec1992	r	14.6±5		q8-24h	x1, q8-24h	NI
5	Kogenate FS	103332	25Feb1993	r	14.6±4	10.7	x1, q8-24h	q6-24h	qod
6	ReFacto	103779	06Mar2000	rb	14.8±6		q8-24h	x1, q8-24h	biwk to tiwk
7	Monoclate-P	103953	17Mar2000	r	17.5		x1, q8-12h	q5hx2 then prn	NI
8	Humate-P	103960	11Apr2000	vpd	12.2		x1, q8-24h	q8-24h	NI
9	Advate	125063	25Jul2003	r	12.03±4	8.9to11.7	q6-24h	x1, q6-24h	qod or q3d
10	Xyntha	125264	21Feb2008	rb	11.2±5	8.03±2	q8-24h	x1, q8-24h	NI
11	NovoEight	125466	15Oct2013	rb	10.83±5		q8-24h	q8-24h	qod to tiwk

pd=plasma derived, v=also indicated for treatment of vWD, r=full-length recombinant FVIII, rb=BDDrFVIII, NI=No Indication for Routine Prophylaxis, NR=Not Reported, #<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm122936.htm>, †as listed on each individual product label, NI=No Indication for Routine Prophylaxis, NR=Not Reported

For products that provide stratification of half-life by age, the average half-life of the FVIII products listed in Table 1 is approximately 14 hours in adults and 10 hours in children. This finding is consistent with the fact that multiple variables, including age, are thought to contribute to the pharmacokinetics of FVIII products in a given patient. Published studies suggest that increased clearance of FVIII in children can result in a shorter half-life of FVIII in the pediatric population compared with adults – although the mechanism by which this occurs is not well understood.^{2,3} For the half-life values listed in Table 1, the recommended dosing frequencies for currently approved FVIII products range from every 5 hours to a single dose for treatment of hemorrhage or perioperative management in surgery. Of the 11 products

² Björkman S, Blanchette VS, Fischer K, et al. Comparative pharmacokinetics of plasma- and albumin-free recombinant factor VIII in children and adults: the influence of blood sampling schedule on observed age-related differences and implications for dose tailoring. *J Thromb Haemost* 2010; 8: 730–736.

³ Barnes C, Lillicrap D, Pazmino-Canizares J, et al. Pharmacokinetics of recombinant factor VIII (Kogenate-FS®) in children and causes of inter-patient pharmacokinetic variability. *Haemophilia* 2006; 12 (Suppl. 4), 40–49.

listed in Table 1, only four are indicated for routine prophylaxis against bleeding with recommended dosing frequencies ranging from every other day to about twice a week. By contrast, the sponsor reports the half-life of Eloctate is about 1½ times longer than that of Advate, a currently available FVIII product. The half-life of Eloctate in adults and adolescents is 16 to 19 hours and 12 to 13 hours in children (Table 2). Eloctate can therefore be dosed less frequently, particularly when used for management of hemorrhage and for routine prophylaxis (Table 2).

Table 2. Half Life and Recommended Dosing Frequency of Eloctate

Product Name	STN	Product Details	Product Half Life (h)†				Recommended Dosing Frequency†		
			>15y n=28	12to<18y n=11	6to<12y n=27	<6y n=10	Hemorrhage	Surgery	Routine Prophylaxis
Eloctate	125487	rb-Fc	19	16.04	13.22	11.54	x1 then q24-48h prn	x1, q8-24h	q3-7d

rb=BDDrFVIII, Fc=fusion protein linked to Fc domain of human IgG1

†as listed on draft product label

1.1.3 Regulatory History

On 23 November 2010, pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb), the FDA granted the sponsor's request for orphan-drug designation of Eloctate for treatment of hemophilia A. The orphan drug designation has been granted to the active moiety of the drug and not the formulation of the drug. The original BLA for Eloctate was submitted to FDA on 07 March 2013 with an initial action due date of 08 March 2014. Following the Mid-Cycle meeting on 27 August 2013, the review committee requested additional information from the sponsor with regard to the proposed process validation protocols. On 15 November 2013, Biogen Idec submitted an amendment (125487/0.27) containing the process validation protocols that will be used to execute the manufacture and control of drug product intermediate strength conformance lots. This submission is classified as a major amendment and has subsequently extended the review period, resulting in a new action due date of 07 June 2014.

1.2 Objectives

This memorandum follows a request from the Office of Blood Research and Review (OBRR) for the Office of Biostatistics and Epidemiology (OBE) to review the available safety related data for Eloctate. As part of this comprehensive safety evaluation, the Pharmacovigilance Plan (PVP) submitted by the sponsor as part of the Risk Management Plan (RMP) for Eloctate has been reviewed, as well as the additional materials listed in Table 3 below.

Table 3. Materials Reviewed

Document Date	Document Type	Document	Source
14Sep2012	Risk Management Plan	Risk Management Plan – version 1. Antihemophilic Factor (Recombinant, Fc Fusion Protein)	Biogen Idec 125487/0
26Aug2013	Information Request	Information Request regarding –b(4)--- and Epidemiology	FDA 125487/0
09Sep2013	Response to Information Request	Response to FDA Request for Information – Epidemiology	Biogen Idec 125487/0.17
05Jan2012	Journal article	Powell JS, Josephson NC, Quon D <i>et al.</i> Safety and prolonged activity of recombinant factor VIII Fc fusion protein in hemophilia A patients. <i>Blood</i> 2012; 119 (13):3031-7	Published literature
Revised Jun2003	Package insert	Enbrel (etanercept) Package Insert	Amgen/Pfizer
Revised May2011	Package insert	Amevive (alefacept) Package Insert	Biogen
Revised Dec2011	Package insert	Orencia (abatacept) Package Insert	Bristol-Myers Squibb
Revised Apr2010	Package insert	Arcalyst (rilonacept) Package Insert	Regeneron Pharmaceuticals
Revised May2013	Package insert	Nplate (romiplostim) Package Insert	Amgen/Pfizer
Revised Apr2013	Package insert	Nulojix (belatacept) Package Insert	Bristol-Myers Squibb
Revised Jun2013	Package insert	Eylea (aflibercept) Package Insert	Regeneron Pharmaceuticals

2. KNOWN SAFETY RELATED INFORMATION

2.1 Known Safety Information for Long-acting BDDrFVIII-Fc Fusion Products

Since Elocbate, if approved, would be the first long-acting BDDrFVIII-Fc fusion product, there is limited safety information about this subset of FVIII products available in the published literature. Safety related information regarding Elocbate, which has been submitted by the sponsor in support of this BLA, is reviewed separately in section 3 below.

A search of the published literature was notable for a study sponsored by Biogen Idec in which the safety of Eloctate was evaluated.⁴ In this study, 16 study subjects received Eloctate and were followed over time for evaluation of safety related endpoints including physical examination, adverse events (AEs), antibody development and laboratory monitoring. A total of 44 AEs were reported by 11 subjects, with 42 AEs considered mild by the study investigators and 2 AEs considered moderate – headache and photophobia. Of note, of the 44 AEs, 21 were reported by a single study subject and were thought by the investigator to be consistent with an anxiety attack. No deaths or serious bleeding episodes were reported and no study subject developed inhibitors to either FVIII or Eloctate. Overall, the authors concluded that Eloctate was well tolerated.

2.2 Known Safety Information for the two components of Eloctate

As the newest subset of the class, little information is available about long acting FVIII products such as Eloctate. Safety related information is however available for the two components of the product – BDDrFVIII products and products fused to the Fc portion of IgG1. This information is reviewed in sections 2.2.1 and 2.2.2 below respectively. Of note, while the safety profile of the two components of Eloctate may be informative, it is important to note that this fusion protein represents a novel molecule which may not function in a manner similar to the individual components.

2.2.1 Known Safety Information for BDDrFVIII products

The B-domain is a large central region of the human FVIII glycoprotein which links two biologically active domains. In BDDrFVIII products, the B-domain is replaced with a short amino acid sequence that links the two biologically active 90-kd and 80-kd domains. An intact full length B-domain is thought to be non-essential for hemostatic effect as both recombinant and plasma-derived FVIII products lacking the B-domain have been shown to be effective in coagulation.⁵ Deletion of the B-domain reduces the size of the glycoprotein resulting in greater ease of manufacturing. In addition, it is thought that deletion of the B-domain confers greater stability on the smaller molecule, eliminating the need for human albumin as a stabilizer and thus reducing the risk of transmission of viral pathogens.⁶

There are currently three BDDrFVIII products approved by FDA (Table 1) – ReFacto, Xyntha and NovoEight. Wyeth improved on ReFacto – the first BDDrFVIII product approved by FDA – by eliminating human albumin from the manufacturing process and by using Chinese Hamster Ovary (CHO) cells grown in the absence of human or animal derivatives. This improved product was named Xyntha. Following Xyntha's approval by the FDA, Wyeth reported their intention for Xyntha to replace ReFacto in the US market, while marketing a similar product ReFacto AF in Europe. Currently Xyntha is the only BDDrFVIII product marketed by Wyeth in the US. NovoEight, a BDDrFVIII product manufactured by Novo Nordisk, was recently licensed by the FDA on 15Oct2013 and is the second BDDrFVIII product marketed in the US. If licensed,

⁴ Powell JS, Josephson NC, Quon D *et al.* Safety and prolonged activity of recombinant factor VIII Fc fusion protein in hemophilia A patients. *Blood* 2012; 119 (13):3031-7

⁵ Sandberg H, Almstedt A, Brandt J *et al.* Structural and Functional Characterization of B-Domain Deleted Recombinant FVIII. *Sem Hematol.* 2001;38(Suppl. 4):4-12.

⁶ Fijnvandraat K, Berntorp E, ten Cate JW *et al.* Recombinant B-domain deleted FVIII (rVIII SQ): pharmacokinetics and initial safety aspects in hemophilia A patients. *Thromb Haemost* 1997; 77 (2):298-302

Eloctate would be the third BDDrFVIII product on the US market and the only long-acting FVIII product licensed by FDA.

Known safety concerns for the entire class of FVIII products – particularly infectivity and immunogenicity – have led to changes in the manufacture of these products over time, culminating in the development of BDDrFVIII products. This evolution in the manufacture of FVIII products is summarized in Table 4 below and the safety concerns of infectivity and immunogenicity are described in sections 2.2.1.1 and 2.2.1.2 below respectively.

Table 4. Summary Timeline of Historical Evolution to BDDrFVIII products^{5, 6, 7, 8}

Date	Event
1960s	Plasma-derived FVIII concentrates become commercially available.
1980s	HIV epidemic results in viral contamination of plasma-derived products and widespread infection of more than half of all hemophiliacs with HIV. ⁷
1990s	Recombinant FVIII products become commercially available and are a popular alternative to plasma-derived concentrates due to the reduced risk of viral transmission. Each generation of recombinant products aims to further reduce the risk of transmission of viral pathogens as follows:
	1 st Generation: Recombinant product produced in hamster cells, use human albumin as a stabilizer
	2 nd Generation: Recombinant product produced in hamster cells, eliminate human albumin as a stabilizer utilizing sterile laboratory-produced stabilizers such as a combination of sucrose and one or more amino acids
	3 rd Generation: Recombinant product produced in cells which are cultured in the absence of human and animal proteins, utilize sterile laboratory-produced stabilizers such as a combination of one or more sugars, amino acids and /or peptides.
2000	The first BDDrFVIII product ReFacto is licensed by FDA.
2008	Xyntha – a BDDrFVIII albumin-free cell culture product is licensed by FDA and replaces ReFacto in the US market.
2013	NovoEight is licensed by FDA and is the second BDDrFVIII product on the US market
2013	Biogen Idec submits an original BLA for Eloctate – a BDDrFVIII long-action Fc fusion product.

2.2.1.1 Transmission of infectious pathogens

Successive generations of FVIII products have sought to reduce the risk of transmission of viral pathogens by moving from plasma-derived to recombinant products and by minimizing the use of human or animal proteins in the manufacturing process (Table 3).

⁷ National Hemophilia Foundation, Blood and Product Safety, HIV/AIDS. Available at: <http://www.hemophilia.org>

⁸ Hoots WK and Shapiro AD. Treatment of Hemophilia. *UpToDate* 2012. Available at <http://www.uptodate.com/contents/treatment-of-hemophilia>.

As with other recombinant products, BDDrFVIII products seek to offer a lower risk of transmission of viral pathogens than plasma-derived products. Like Xyntha and NovoEight, Eloctate will be a 3rd generation recombinant FVIII product – that is, a recombinant product manufactured in the absence of human and other animal derived-components to reduce the risk of transmission of infectious pathogens.

2.2.1.2 Immunogenicity – FVIII inhibitors and Antibodies to non-human proteins

Published studies sponsored by Wyeth have evaluated the currently licensed Wyeth BDDrFVIII products for immunogenicity with regard to the development of both FVIII inhibitors and antibodies to non-human proteins. In addition, NovoNordisk has provided information regarding immunogenicity in support of the BLA for NovoEight. These findings are summarized in sections 2.2.1.2 (a) and 1.2.1.2 (b) below.

2.2.1.2 (a) FVIII inhibitors

The development of FVIII inhibitors has long been recognized as a safety concern for the class of FVIII products. While the etiology of the development of inhibitors to FVIII has not been fully elucidated, it is thought to result from a host alloimmune response to infusions of FVIII.

Deletion of the B-domain results in a novel peptide sequence not found in plasma-derived FVIII. Early concerns that this novel sequence might function as an antigenic epitope and provoke increased production of antibodies to the BDDrFVIII molecule have not been borne out in clinical studies. An open-label observational study of Wyeth's licensed BDDrFVIII products followed 113 severe hemophiliacs who were previously treated patients (PTPs) for a period ranging from 12 months up to 5 years and found an incidence of inhibitor formation of 0.9% following the use of BDDrFVIII products, consistent with that reported for full-length recombinant and plasma derived FVIII products.⁹ A similar study evaluated previously untreated patients (PUPs). In an open-label multicenter study, 101 PUPS received prophylactic and/or treatment doses of BDDrFVIII products for a period ranging from 50 exposure days (ED) up to 5 years. Thirty-two percent of patients developed inhibitors, a rate comparable to that seen with full-length recombinant products.¹⁰

Prelicensure studies submitted by NovoNordisk in support of licensure for NovoEight, were similarly reassuring. Of 214 PTPs, only 1 study subject was found to have a single low titer inhibitor test.¹¹ The study subject was negative for inhibitors on repeat testing and had no clinical evidence of bleeding. Evaluation of inhibitor development in PUPs receiving NovoEight is planned in the postmarketing study NN7008-3809.

2.2.1.2 (b) Antibodies to non-human proteins

⁹ Courter SG and Bedrosian CL. Clinical Evaluation of B-Domain Deleted Recombinant FVIII in Previously Treated Patients. *Sem Hematol.*2001;38 (Suppl. 4):44-51 (Protocol 3082A1-300-WW, Final study report, eCTD 103779/5089)

¹⁰ Courter SG and Bedrosian CL. Clinical Evaluation of B-Domain Deleted Recombinant FVIII in Previously Untreated Patients. *Sem Hematol.*2001;38 (Suppl. 4):52-9. (Protocol 3082A1-301-WW, Final study report, eCTD 103779/5089)

¹¹ NovoNordisk. Complete Study Report Pivotal trial NN7008-3545 08Feb 2012. eCTD 125466/0

Another more recent safety concern has been the detection of antibodies to non-human proteins in subjects treated with recombinant biologics. It appears for instance, that even minor amounts of CHO proteins in the final formulation of therapeutics can potentially stimulate an immune response. The clinical significance of the presence of these antibodies is unclear. It has however been suggested that any regions of these mammalian proteins that are homologous to human sequences may stimulate an immune response resulting in inhibition of the active pharmaceutical ingredient and perhaps diminish both the safety and efficacy of the final recombinant product.¹²

Unlike both Xyntha and NovoEight which are produced in CHO cells, Eloctate is produced in HEK cells thus eliminating a potential source of non-human mammalian proteins with antigenic potential.

In summary, the available published literature suggests that when evaluated for the known safety concerns for the class of FVIII products, such as risk of infection and immunogenicity, BDDrFVIII products have a safety profile comparable to or better than that of other products in the class.

2.2.2 Known Safety Concerns for Fc fusion products

There have been seven Fc fusion protein products approved by the FDA (Table 5 below). An eighth product – Alprolix is currently under review. The first Fc fusion product, Enbrel (etanercept), was approved in 1998 and the last two products were approved in 2011.¹³ Most of these products are fused to lymphocyte immunomodulating agents for the treatment of inflammatory diseases such as rheumatoid arthritis, psoriasis or rejection of transplanted organs. Because these immunomodulators can affect the host immune system, the package inserts (PIs) for these products include warnings regarding the risk of serious infections and/or the development of hematologic malignancies.

Of the eight Fc fusion proteins currently approved or under review by FDA, two products – Nplate and Alprolix – are similar to Eloctate in that the Fc portion of IgG1 is bound to a functional peptide rather than a lymphocyte immunomodulator. While Eloctate is an Fc fusion with FVIII, Nplate is a fusion with a thrombopoietin analogue peptide and is indicated for treatment of thrombocytopenia. Nplate's PI does not list infection as a risk, presumably because the potential effects of the Fc portion alone were not found to significantly affect the host immune response to infection. The risks of acute myelogenous leukemia (AML), thrombotic complications and changes in bone marrow morphology are listed on the Nplate PI. The risk of hematologic abnormalities may result from Nplate's mechanism of action – the activation of transcriptional pathways that stimulate increased bone marrow production of platelets. This effect is mediated by the thrombopoietin analogue moiety of the product, rather than the Fc portion of Nplate, making it unlikely that this particular risk factor would be conferred to Eloctate.

¹² Gutiérrez AH, Moise L and De Groot AS. Human Vaccines: News and Views. Of [hamsters] and men – A new perspective on host cell proteins. *Human Vaccines* 2012; 8:1172-1174; September 2012

¹³ Czajkowsky DM, Hu J, Shao Z, Pleass RJ. Fc-fusion proteins: new developments and future perspectives. *EMBO Mol Med.* 2012 Oct;4(10): 1015-28.

Of all the Fc fusion proteins, Alprolix is perhaps the most similar to Eloctate in that Alprolix is a fusion with recombinant coagulation Factor IX (FIX) and is also produced by Biogen Idec. If approved, Alprolix would be indicated for treatment of FIX deficiency or Hemophilia B. The FDA's review of Alprolix's BLA is currently underway. However, at this time the available safety data do not appear to indicate a specific safety concern requiring a Postmarketing Requirement (PMR) or Risk Evaluation and Mitigation Strategy (REMS).

Table 5. Fc fusion products approved or currently under review by FDA^{13, 14}

	Product Name	Moiety fused to the Fc portion of human IgG1	Indication	Year of FDA Approval	Sponsor
1	Enbrel (etanercept)	Tumor Necrosis Factor Receptor (TNFR)	Rheumatoid arthritis	1998	Amgen/Pfizer
2	Amevive (alefacept)	Lymphocyte Function Associated Antigen 3 (LFA-3)	Psoriasis and transplant rejection	2003	Astellas Pharma Biogen Idec
3	Orencia (abatacept)	Mutated Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4)	Rheumatoid arthritis	2005	Bristol-Meyers Squibb
4	Arcalyst (rilonacept)	Interleukin-1 Receptor (IL-1R)	Cryopyrin-associated periodic syndromes	2008	Regeneron Pharmaceuticals
5	Nplate (romiplostim)	Thrombopoietin-binding peptide	Thrombocytopenia due to chronic immune thrombocytopenic purpura	2008	Amgen/Pfizer
6	Nulojix (belatacept)	CTLA-4	Organ rejection	2011	Bristol-Meyers Squibb
7	Eylea (afibercept)	Vascular Endothelial Growth Factor Receptor 1/2 (VEGFR1/VEGFR2)	Age related macular degeneration	2011	Regeneron Pharmaceuticals
8	Alprolix (rFIX-Fc)	Coagulation Factor IX (recombinant)	Hemophilia B	Pending	Biogen Idec

Of note, all the licensed Fc fusion products include sections in the PI evaluating immunogenicity and antibody formation. The incidence of antibody formation varies from <5% to 35% depending on the particular product and the assay used to detect antibodies. Findings for Nplate and Alprolix were similar to the rest of the products in the class. Other than two patients (0.4%) in the Nplate trial who developed antibodies with neutralizing activity, the rest of the antibodies developed by study subjects did not demonstrate any correlation with clinical effectiveness or

¹⁴ BBaer. Medical Officer, PVB/DE/FDA. Personal Communication and Alprolix PVP Review Memo 20130808 (Draft)

any specific safety concern.¹⁵ In the case of Alprolix, of the four study subjects who tested positive for anti-FIX antibodies during the clinical trial 998HB102, all four had tested positive for these antibodies prior to receipt of Alprolix.¹⁴

A review of the regulatory history of the two products most similar to Elocbate was notable for a REMS required for Nplate at the time of product approval in 2008. The REMS included restricted distribution of the product and additional safety data collection requirements to ensure that the benefits of the drug outweigh the risks which include development of AML, thrombotic complications and changes in bone marrow morphology.¹⁶ Upon further review, FDA and Amgen determined that information collected through the REMS was confounded by underlying medical conditions in the treated patient population, and could not be used to determine the precise role of Nplate in the development of the adverse events. For this reason on 06 December 2011, the REMS was modified so that enrollment of prescribers, patients and institutions and mandatory collection of safety data is no longer required. Although the review of Alprolix is currently underway and as yet incomplete, at this time the available safety data do not appear to indicate a specific safety concern necessitating either a REMS or PMR.

In summary, a review of the safety profile and regulatory history of Fc fusion products similar to Elocbate suggests that while these products may carry a risk of infection or hematologic malignancy, these risks are thought to result from the immunomodulatory moieties of the product rather than the Fc portion itself. In addition, evaluation of the two Fc fusion products most similar to Elocbate indicates that both Nplate and Alprolix have an incidence of antibody formation similar to that of other products in the class. Furthermore, review of the regulatory history of these two products does not indicate specific safety concerns or any ongoing safety related regulatory action.

3. PHARMACOVIGILANCE PLAN REVIEW

3.1 Clinical Safety Database

The overall clinical development program submitted by Biogen Idec for Elocbate consists of a total of four clinical trials (Table 6). Of these four trials, two have been completed in the prelicensure phase and two will be continued in the postlicensure phase.

¹⁵ Amgen. Nplate (romiplostim) Highlights of Prescribing Information. Revised May 2013

¹⁶ FDA Drug Safety Communication: Modified Risk Evaluation and Mitigation Strategies (REMS) for Nplate (romiplostim) and Promacta (eltrombopag). 06Dec2011. Available at <http://www.fda.gov/Drugs/DrugSafety/ucm280165.htm>

Table 6. Study Subjects Enrolled in Prelicensure Studies of Eloctate

	997HA301	998HA101	8HA02PED	8HA01EXT
Study Type	Pivotal Trial	Single Dose Trial	Pediatric Trial	Extension Trial
Study Status	Complete	Complete	Ongoing	Ongoing
Study Description	Phase 3 Study of Safety, Tolerability, Efficacy and PK of repeat doses	Phase 1/2a Study of Safety, Tolerability and PK of single dose	Pediatric Study of Safety, Efficacy and PK of repeat doses	Extension Study of long term Safety and Efficacy
Study Subjects (n)	165	16	23*	150^

*as of 04Jan2013, ^as of 07Jan2013

All four clinical trials have safety related endpoints. The Pivotal trial 997HA301 and Single Dose trial 998HA101 have been completed and final study reports have been submitted with the BLA. The Pediatric and Extension trials are currently ongoing and interim study reports have been submitted by the sponsor. All four reports have been reviewed and are summarized in section 3.1.1 below. The two ongoing trials - 8HA02PED and 8HA01EXT, are listed in the Pharmacovigilance Plan (PVP) along with other planned pharmacovigilance activities. The PVP is reviewed in detail in section 3.2 below.

3.1.1 Prelicensure Clinical Trial Safety Information

The sponsor has provided study reports for all four clinical trials conducted in support of the BLA. The safety related data for these four trials is summarized in Sections 3.1.1.1, 3.1.1.2, 3.1.1.3 and 3.1.1.4 below.

3.1.1.1 Safety related data from Pivotal trial 997HA301

The prelicensure Pivotal trial 997HA301 has been completed by the sponsor. The final study report has been reviewed and safety related data is summarized in Table 7 below.

Table 7. Summary of Pivotal trial 997HA301

Study Title:	A-LONG: Open-label, Multicenter Evaluation of Safety, PK and Efficacy of Eloctate in Prevention & Treatment of Bleeding in PTPs with severe Hemophilia A	
Study Design:	Phase 3 multi-center, multi-national, open label, 3 arm trial for 3 dosing regimens:	
	<u>Arm 1:</u>	Individualized prophylaxis - 25 IU/kg on D1, 50 IU/kg on D4 then individualized dose of 25 IU/kg to 65 IU/kg q 3 to 5D to maintain a trough level of 1% to 3% FVIII activity (or higher, if clinically indicated) for ≥ 50 ED.
	<u>Arm 2:</u>	Weekly Prophylaxis - 65 IU/kg q 7D for 50 ED or until end of study
	<u>Arm 3:</u>	On-Demand Dosing - Initial single dose of 50 IU/kg then 10 to 50 IU/kg prn bleeding depending on the severity of bleeding.
	<u>Surgical Subgroup:</u>	Subjects from any arm who had major surgery during the study. Subjects switched to prescribed perioperative management dose until investigator deemed that it safe to return to assigned treatment arm.
Eligibility criteria:	Male severe (FVIII \leq 1%) hemophiliacs aged 12 to 65 years, No history of inhibitors (\geq 0.6 BU/mL), PTPs with \geq 150 ED to any FVIII product. No IVIg use or renal or hepatic dysfunction and:	
	Arm 1:	on a prophylaxis regimen prior to study entry

	Arm 2:	on an episodic regimen prior to study entry. These study subjects were randomized to either Arm 2 or 3 based on individual annualized bleeding episodes in the 12 months prior to study entry.				
	Arm 3:					
	Surgical Subgroup:	received at least 12 rFVIIIFc EDs in any Arm of the trial and tested negative for inhibitors after at least 12 rFVIIIFc EDs and within 4 weeks prior to surgery				
Study Duration:	29Nov2010 to 06Aug2012					
Study Status:	Complete. Final study report submitted.					
Primary Objectives:	<ul style="list-style-type: none">To evaluate safety and tolerability of rFVIIIFc (all Arms)To evaluate efficacy of rFVIIIFc tailored prophylaxis regimen (Arm 1) on-demand therapy (Arm 3) and perioperative management (Surgical Subgroup)					
Secondary Objectives:						
Safety related endpoints:	AE and PE monitoring Incidence of inhibitor development					
Study Population:		Arm 1	Arm 2	Arm 3	Surgical Subgroup	Total (Arm1+2+3)
	Entered (n):	118	24	23	9	165
	Completed (n):	112	19	22	9	153
	Surgery patients (n):	8	1	0	9	9
	Age (years):					
	Median	29.0	31.5	34.0	36.0	30.0
	Range	12-65	18-59	13-62	26-56	12-65
	Race(n):					
	White	79	12	16	7	107
	Black/AfAm	7	1	2	1	10
	Asian	27	11	5	1	43
	Other	5	0	0	0	5
Study Results:	AE monitoring	17 SAEs reported in 12 of 165 subjects (7.3%). 2 SAEs reported by 2 of 9 surgical subjects (22.2%). No individual SAE reported by more than 1 subject. 1 death was reported in a patient with history of depression and drug abuse.				
	PE	1 report of perianal venous thrombosis or hemorrhoid				
	Laboratory parameters	No FVIII inhibitors were detected. 1 subject tested positive for inhibitors but was negative on repeat testing. No effect on IgIV levels				
Conclusion:	No clinically significant safety issues were identified					

3.1.1.1 (a) Death in Pivotal trial 997HA301

The death reported in the Pivotal Study 997HA301 was reviewed in detail and is summarized below.

Subject 905-002: 20 yo White man enrolled in Arm 1 with a past medical history of depression and substance abuse was reported to be depressed with slurred speech on study Day 235. The following day, the subject was found dead at his home. Comprehensive postmortem toxicology studies showed overdose with alprazolam, methadone, morphine, sertraline, and marijuana. The death certificate and autopsy ruled the death a suicide from polysubstance overdose.

3.1.1.1. (b) Transient FVIII inhibitor in Pivotal trial 997HA301

A single study subject tested positive for FVIII inhibitor but was negative on repeat testing and therefore did not meet the prespecified definition of positive for FVIII inhibitor.

Subject 900-010: 25 yo White man enrolled in Arm 1 had an unconfirmed positive inhibitor test result of 0.73 BU at Week 14 and had negative results on repeat testing 18 days later and subsequent tests at Week 28 and Week 34. This patient also tested positive for anti-rFVIII Fc antibody (Section 3.1.1.1 (c) below). The subject had no clinical sequelae of bleeding and reported no AE at all during the study.

3.1.1.1 (c) Anti-Eloctate antibody (also known as anti-rFVIII Fc or anti-drug antibodies, ADA) in Pivotal trial 997HA301

A total of five subjects tested positive for ADA at screening, prior to the first dose of Eloctate (Subjects 180-002, 340-001, 344-001, 401-001, and 500-011). Of these five subjects, only one reported an AE during the study – subject 344-001 reported fever. In all cases ADA titers declined during the course of the study and the antibody was no longer detected in two of the five subjects at the final visit.

In addition, six subjects had negative ADA tests at screening and positive results after the first dose of Eloctate (Subjects 120-001, 321-003, 423-001, 900-010, 938-001, and 938-002). Of these six subjects, three reported AEs, none of which were consistent with hemorrhage or bleeding.

The 11 subjects with ADA positive tests either at screening or during the study, do not share a pattern of AEs suggestive of a common clinical syndrome.

3.1.1.1 (d) Thrombotic Events (TE) in Pivotal trial 997HA301

A single study subject reported a mild venous thrombosis

Subject 301-002: 41yo Male in Arm 1 experienced mild venous thrombosis on Study Day 197 (after receiving 74 Eloctate injections). The study investigator reported perianal venous thrombosis and treatment included topical lidocaine ointment rectally. The event was considered resolved on Study Day 201 while the subject continued in the study and was assessed as unrelated to Eloctate treatment by the Investigator. The subject received an additional 12 injections of Eloctate and completed the study. The sponsor suggests the event was likely a rectal hemorrhoid.

3.1.1.2 Safety related data from Single Dose trial 997HA101

The prelicensure Pivotal trial 997HA101 has been completed by the sponsor. The final study report has been reviewed and safety related data is summarized in Table 8 below.

Table 8. Summary of Single Dose trial 997HA101

Study Title:	Open-Label, Crossover, Dose-Escalation, and Multi-Center Study to Determine the Safety, Tolerability, and Pharmacokinetics of a Single Intravenous Injection of rFVIII Fc in PTPs with Severe Hemophilia A	
Study Design:	Phase I/IIa, Open-Label, Crossover, Dose-Escalation, Multi-Center Study	
Eligibility criteria:	Male severe (FVIII \leq 1%) hemophiliacs aged \geq 12 years, No history of inhibitors (\geq 0.6 BU/mL), PTPs with \geq 100 ED to any FVIII product. No coagulopathy other than Hemophilia A. No severe renal or hepatic dysfunction. HIV negative or HIV positive with CD4 \geq 200	
Study Duration:	11Dec2009 to 06Jul2010	
Study Status:	Complete. Final study report submitted.	
1° Objectives:	<ul style="list-style-type: none"> To assess the safety and tolerability of single administration of two doses of Eloctate (25 and 65 IU/kg) 	
2° Objectives:	<ul style="list-style-type: none"> To characterize the PD and PK of Eloctate compared to Advate. 	
Safety related endpoints:	AE and PE monitoring Incidence of inhibitor development and anti-rFVIII Fc antibody	
Study Population	Total Subjects Enrolled (n):	19
	Completed Trial (n):	16
	Age (years):	
	Median	30.5
	Range	23-61
	Race (n):	
	White	15
	Black/AfAm	0
	Asian	1
	Other	0
Study Results:	AE monitoring	No SAE or deaths reported.
	PE	No evidence of malignancies
	Lab parameters	No FVIII inhibitors or anti-rFVIII Fc antibodies detected
Conclusion:	No clinically significant safety issues were identified	

3.1.1.3 Safety related data from Pediatric Trial 8HA02PED

The Pediatric trial 8HA02PED was conducted prelicensure and will continue in the postmarketing phase. The interim study report has been reviewed and safety related data is summarized in Table 9 below.

Table 9. Summary of Pediatric Trial 8HA02PED

Study Title:	An Open-Label, Multicenter Evaluation of Safety, Pharmacokinetics, and Efficacy of Recombinant Coagulation Factor VIII Fc Fusion Protein in the Prevention and Treatment of Bleeding Episodes in Pediatric Subjects With Hemophilia A	
Study Design:	Phase 3 Open-Label, Multi-Center Study	
Eligibility criteria:	Male severe (FVIII $<$ 1%) hemophiliacs aged $<$ 12 years, No history of inhibitors (\geq 0.6 BU/mL), PTPs with \geq 50 ED to any FVIII product. No coagulopathy other than Hemophilia A. No severe renal or hepatic dysfunction. HIV negative or HIV positive with CD4 \geq 200	
Study Duration:	27Aug2012 to ongoing	

Study Status:	Ongoing. Interim study report as of 07Jan2013 submitted. Final study report to be submitted after goal enrollment and data collection criteria met ie PK data for 12 subjects <6yo and 12 subjects 6 to <12yo, ≥50 ED and inhibitor testing for ≥50 subjects.	
1° Objectives:	<ul style="list-style-type: none"> To evaluate the safety of rFVIII-Fc in pediatric PTPs with hemophilia A 	
2° Objectives:	<ul style="list-style-type: none"> To evaluate the PK, consumption and efficacy of rFVIII-Fc for prevention and treatment of bleeding episodes. To evaluate the effect of rFVIII-Fc based on patient-reported outcomes and health outcomes. 	
Goal enrollment:	Total of 50 subjects – 25 subjects <6 yo and 25 subjects 6 to <12 yo	
Safety related endpoints:	AE and PE monitoring. Incidence of inhibitor development, allergic reactions and TE	
Study Population: (as of 04Jan2013)	Study subjects enrolled :	(n)
	Total:	33
	Received ≥ 1dose of Eloctate:	23
	Yet to receive Eloctate:	10
	Discontinued:	0
	Age (years):	
	<6	11
	6 to <12	22
	Race:	
	White	19
	Black/AfAm	7
Study Results: (as of 07Jan2013)	AE monitoring	1 SAE of a device related infection was reported. No deaths
	PE	No evidence of TE, anaphylaxis or serious hypersensitivity.
	Lab parameters	No FVIII inhibitors detected
Conclusion:	No clinically significant safety issues were identified	

3.1.1.3 (a) Serious Adverse Event in Pediatric trial 8HA02PED

One SAE was reported in the Pediatric trial 8HA02PED and is reviewed in detail below.

Subject –b(6)--: 8 yo male with a past medical history of iron deficiency was hospitalized on study Day 1 for a device-related infection. The subject was treated with antibiotics and removal of the infected portacath, and the event resolved.

3.1.1.4 Safety related data from Extension Trial 8HA02EXT

The Extension trial 8HA02EXT was conducted in the prelicensure phase and the sponsor intends to continue the study postmarketing should this BLA be approved. The interim study report has been reviewed and safety related data is summarized in Table 10 below.

Table 10. Summary of Extension Trial 8HA02EXT

Study Title:	An Open-Label, Multicenter Evaluation of the Long-Term Safety and Efficacy of Recombinant Human Coagulation Factor VIII Fusion Protein (rFVIII-Fc) in the Prevention and Treatment of Bleeding Episodes in Previously Treated Subjects With Hemophilia A
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Study Design:	Phase 3 Open-Label, Multi-Center Extension of the Pivotal trial 997HA301 and the Pediatric trial 8HA02PED. Subjects will follow dosing regimen based on the clinical profile observed in the preceding study and can change dosing regimens based on the assessment of the study investigator. Subjects who require surgery may be treated with the dosage regimen deemed appropriate for the type of surgery.			
Eligibility criteria:	Study subjects who have completed the Pivotal trial 997HA301 or Pediatric trial 8HA02PED and have no history of high titer FVIII inhibitor (≥ 5 BU). Study subjects will continue for ≤ 4 years and approximately ≥ 50 ED or until Elocbate is commercially available in the applicable participating country.			
Study Duration:	15Dec2011 to ongoing			
Study Status:	Ongoing. Interim study report as of 07Jan2013 submitted. Final study report to be submitted depending on marketing approval.			
1° Objectives:	<ul style="list-style-type: none">To evaluate long term safety of rFVIIIc in PTPs with hemophilia ATo evaluate efficacy of rFVIIIc in prevention and treatment of bleeding			
2° Objectives:				
Goal enrollment:	Total of 194 subjects – 144 subjects from Pivotal trial 997HA301 and 50 from Pediatric trial 8HA02PED			
Safety related endpoints:	AE and PE monitoring. Incidence of FVIII inhibitor development, allergic reactions and Thrombotic Events (TE)			
Study Population: (as of 07Jan2013)	Study subjects enrolled from :		Pivotal Trial (n)	Pediatric Trial (n)
	Total:		150	0
	Received ≥ 1 dose of Elocbate:		150	0
	Yet to receive Elocbate:		0	0
	Discontinued:		1	0
	Age (years):			
	<18		11	0
	6 to <12		139	0
	Race:			
	White		98	0
	Black/AfAm		8	0
	Asian		39	0
	Other		5	0
Study Results: (as of 07Jan2013)	AE monitoring	10 SAE in 8 subjects -hydrocephalus, head injury, spinal osteoarthritis, hemorrhagic gastritis, joint dislocation, dehydration, device dislocation, post-procedural hemorrhage, depression, and traumatic hematoma. No deaths		
	PE	No evidence of TE, anaphylaxis or serious hypersensitivity.		
	Lab parameters	No FVIII inhibitors detected		
Conclusion:	No clinically significant safety issues were identified			

3.1.1.4 (a) Serious AEs in Extension trial

A total of ten AEs were reported by eight study subjects. These events were reviewed in detail and are summarized below.

Subject 500-006 (Head injury): 49yo Male with past medical history of hemophilic arthropathy and hypertension hit his head upon standing and sustained an 18 cm open head wound requiring sutures. The subject was observed overnight and discharged the following day with resolution of the event.

Subject 584-001 (Joint dislocation): 49yo Male with a past medical history of HIV reported right patellar dislocation requiring splinting and pain medication.

Subject 901-001 (Dehydration): 43yo Male with viral flu and vomiting was hospitalized for dehydration treated medically and discharged the same day.

Subject 902-004 (Depression): 17yo male with history of depression was hospitalized for depression and aspirin overdose. The subject was eventually discharged home and the event resolved.

Subject 924-003 (Traumatic hematoma): 28yo male with a history of hepatitis C, was hospitalized for abdominal hematoma after he was hit by his son in the abdomen. He was eventually discharged home and the event was resolved.

Subject 344-003 (Hydrocephalus): 25yo male with a history of hydrocephalus (diagnosed during previous Study 997HA301) was hospitalized for ventriculostomy and further evaluation. The subject was discharged and symptoms improved.

Subject 500-008 (Spinal osteoarthritis and Gastritis hemorrhagic): 55yo male with a history of HIV was hospitalized for spinal osteoarthritis on study Day 14 and for hemorrhagic gastritis on study Day 179. Both events resolved.

Subject 901-002 (Device dislocation and Post-procedural hemorrhage): 44yo male was hospitalized for dislocation of a prosthetic left knee requiring arthroplasty. The subject was discharged the day following the procedure and subsequently readmitted later that day for post-procedural hemorrhage. The subject required no blood product transfusions and the hematocrit remained stable throughout both hospitalizations.

3.1.2 Limitations of the Clinical Safety Database

3.1.2.1 Predominance of male gender

All patients evaluated in the clinical safety database are male hemophiliacs. As a result, experience regarding the use of this product in female hemophiliacs and during pregnancy or lactation is limited. However, given the rarity of female hemophiliacs, the gender demographic of the clinical safety database likely reflects the target population in which this product will be used.

3.1.2.2 Relatively low risk population for development of FVIII inhibitors

The sponsor reports that no study subjects developed FVIII inhibitors. While the etiology of the development of FVIII inhibitors has not been fully elucidated, risk factors are thought to include a family history of inhibitors, nonwhite ethnicity and severe disease requiring intense replacement therapy.¹⁷ Although all patients in the clinical safety database are severe hemophiliacs, subjects with a history of inhibitors were excluded and the majority of patients reported their ethnicity as

¹⁷ Hoots WK and Shapiro AD. Factor VIII and factor IX inhibitors in patients with hemophilia. *UpToDate* 2013. Available at <http://www.uptodate.com/contents/factor-viii-and-factor-ix-inhibitors-in-patients-with-hemophilia>

white. Thus, with regard to the development of FVIII inhibitors, the risk profile of the population in which the product has been used so far, may not be representative of the wider target population.

3.1.2.3 Limited use in surgery

A total of 9 surgical patients, most of whom were White, were evaluated in the Pivotal trial. The median age of the surgical patients was 36.0 years of age with ages ranging from 26 to 56 years old. Thus the experience of use of Eloctate in surgical patients is limited by the small number of surgical patients, the predominance of white ethnicity and the absence of young children in this subset of study subjects.

3.1.2.4 Exclusive experience in PTPs

All study subjects in the clinical safety database are PTPs. This is however consistent with recommendations from the European Medicines Agency (EMA) and the International Society on Thrombosis and Hemostasis (ISTH) regarding the use of PTPs as study subjects in prelicensure studies. PTPs, by virtue of not having developed an inhibitor, are generally considered to be tolerant of factor VIII and therefore at a relatively low risk for inhibitor development. The EMA therefore recommends that prelicensure trials to evaluate the immunogenicity of new products should include PTPs since excessive inhibitor formation in PTPs would suggest increased immunogenicity of the product.¹⁸ Because of the rarity of PUPs and the fact that PUPs have a certain – but not clearly defined – likelihood of inhibitor formation, the ISTH recommends that PUPs should be reserved for studies of the natural history of inhibitor development.¹⁹ There is currently no experience with the use of Eloctate in PUPs.

3.2 Pharmacovigilance Plan

Following review of the initial Pharmacovigilance Plan (PVP) proposed by Biogen Idec (125487\0), FDA requested clarification regarding the sponsor's planned actions for specific safety concerns, and Biogen Idec agreed to add four additional safety concerns (125487\0.17) to the PVP – Development of non-neutralizing antibodies to rFVIII¹⁸Fc, Dosing errors, Use in pregnancy and lactation and Use in PUPs. The most recent version of the PVP proposed by the sponsor (125487\0.32), includes the additional safety concerns and is summarized in Table 11 below. The two studies listed in the PVP, the Pediatric Study 8HA02PED and the Extension Study 8HA01EXT, have been reviewed and summarized in Table 9 and 10 above respectively.

¹⁸ European Medicines Agency. Preauthorisation Evaluation of Medicines for Human Use, London 22 February 2007. Report on Expert Meeting on factor VIII products and inhibitor development. 28 February 2006-2 March 2006. Available at: http://www.emea.europa.eu/docs/en_GB/document_library/Report/2009/11/WC500015512.pdf

¹⁹ White GC, DiMichele D, Mertens K *et al* Utilization of Previously Treated Patients (PTPs), Noninfected Patients (NIPs), and Previously Untreated Patients (PUPs) in the Evaluation of New Factor VIII and Factor IX Concentrates. Recommendation of the Scientific Subcommittee on Factor VIII and Factor IX of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. *Thromb Haemost* (1999)81:462

Table 11. Summary of Pharmacovigilance Plan

Safety Concern	Planned action(s)
Important Identified Risks	
None	N/A
Important Potential Risks	
Inhibitor (neutralizing antibody) development	<ul style="list-style-type: none"> • Routine pharmacovigilance activities including Pediatric Trial 8HA02PED and Safety Extension Trial 8HA01EXT • Enhanced pharmacovigilance activities
Allergic Reaction or Anaphylaxis	<ul style="list-style-type: none"> • Routine pharmacovigilance activities including Pediatric Trial 8HA02PED and Safety Extension Trial 8HA01EXT • Enhanced pharmacovigilance activities
Development of anti-FVIII (non-neutralizing antibodies) to rFVIII-Fc	<ul style="list-style-type: none"> • Routine pharmacovigilance activities including antibody testing in Pediatric Trial 8HA02PED and Extension Trial 8HA01EXT • Enhanced pharmacovigilance
Dosing errors	<ul style="list-style-type: none"> • Routine pharmacovigilance activities including Pediatric Trial 8HA02PED and Extension Trial 8HA01EXT • Enhanced pharmacovigilance
Important Missing Information	
Safety profile in patients ≥ 65 years old	<ul style="list-style-type: none"> • Routine pharmacovigilance activities including limited data from Safety Extension Trial 8HA01EXT
Safety profile in children <12 years old	<ul style="list-style-type: none"> • Routine pharmacovigilance activities including Pediatric Trial 8HA02PED and potentially limited data from Safety Extension Trial 8HA01EXT
Use of rFVIII-Fc in pregnancy and lactation	<ul style="list-style-type: none"> • Routine pharmacovigilance
Use of rFVIII-Fc in previously untreated patients (PUPs)	<ul style="list-style-type: none"> • Routine pharmacovigilance • Future Postmarketing Study in PUPs

Routine pharmacovigilance is described by the sponsor as cumulative analyses in Periodic Safety Update Reports as well as the two studies - Pediatric Trial 8HA02PED and Safety Extension Trial 8HA01EXT. Enhanced pharmacovigilance activities are described by the sponsor as expedited reporting to regulators of an inhibitor and targeted follow up by questionnaire of the AE of interest in spontaneous reports, other programs where data are being handled or solicited and all clinical trial SAEs.

Study milestones for the two ongoing studies included in the PVP have been provided and are listed in Table 12 below.

Table 12. Estimated Milestones for Pediatric Trial 8HA02PED and Extension Trial 8HA01EXT

Milestone	Estimated Date	Comments
Pediatric Trial 8HA02PED		
Last patient in	November 2013	
Clinical study report (CSR)	September 2014	No interim CSR planned
Extension Trial 8HA01EXT		
Last patient in	April 2014	Last subject from pediatric study (8HA02PED)
Interim CSR	September 2014	Interim analysis planned to support EU MAA submission
Final CSR	December 2019	Final CSR date will be driven by the study completion date in the last participating

3.2.1 Limitations of the Pharmacovigilance Plan

3.2.1.1 Theoretical Risk of Thrombotic Events (TE)

Since Eloctate would be the first long-acting FVIII product on the market, dosing errors may occur where the product is given more frequently than recommended and dosing errors of this type may result in elevated FVIII levels. While elevated FVIII levels have been shown to be a risk factor for venous TE in non-hemophiliacs,²⁰ it is unclear whether elevated FVIII levels can result in TE in patients with hemophilia A. The development of TE after Eloctate may therefore be a theoretical risk given the potential for dosing errors with the first long-acting FVIII product. It is however, reassuring that no medically confirmed TE were identified in the prelicensure trials, and that any adverse events resulting from dosing errors including potential TE, will be addressed in the PVP through the ongoing clinical trials as well as with both routine and enhanced pharmacovigilance.

3.2.1.2 Use in PUPs

Limitations of the prelicensure clinical safety database include exclusive experience in PTPs (Section 3.1.2 above). As a result, information regarding the use of this product in PUPs have not been addressed in the prelicensure studies. Although the sponsor plans a postmarketing study in PUPs, limited information has been provided to date regarding the planned study.

3.2.1.3 Long-term evaluation of safety

The sponsor lists the Extension trial 8HA01EXT in the PVP as the planned action for the long-term evaluation of the safety of Eloctate. However, the planned duration of the trial is ≤ 4 years or until Eloctate is commercially available in the applicable participating country. Because the study duration is dependent upon the date of licensure, the study may last significantly less than 4 years, in which case the study would fail to meet the primary objective to evaluate the long-term safety of this product. When asked to clarify this point, the sponsor reports that pediatric patients enrolled in the Pediatric Trial 8HA02PED, will be followed for at least 100 ED in the Extension Trial 8HA01EXT regardless of when the product becomes commercially available in the study subject's country. In addition, the sponsor notes that while a subset of subjects will not complete 4 years of participation in the Extension Trial, it is estimated that nearly all subjects across all

²⁰ Ota S, Yamada N, Ogihara Y *et al.* High Plasma Level of Factor VIII – an important risk factor for Venous Thromboembolism. *Circ J* 2011; 75(6):1472-5

age groups will be followed long term on Eloctate. The sponsor estimates that approximately 200 subjects (including 60 pediatric subjects) will achieve 100 ED to Eloctate and that 100 subjects will participate in the Extension Trial for 3 years or more and 40 subjects for 4 years or more. The sponsor does not report on the means by which these estimates are reached.

4. INTEGRATED RISK ASSESSMENT

The available data submitted by the sponsor in support of this BLA have evaluated two of the known safety concerns for the class of FVIII products – infectivity and immunogenicity. There were no AEs reported that were consistent with transmission of an infectious agent. As a 3rd generation recombinant FVIII product, Eloctate carries minimal risk of transmission of infectious agents such as Hepatitis viruses or HIV.

With regard to immunogenicity, 1 study subject had a single low titer inhibitor test which was negative on repeat testing and the patient had no clinical evidence of bleeding (Section 3.1.1.1 (b)). Thus no study subjects met the prespecified study definition of FVIII inhibitor development. Although this finding is reassuring, the limitations of the clinical safety database with regard to development of FVIII inhibitors (Section 3.1.2) must be considered when interpreting these results.

Of the 11 patients in the clinical development program, who tested positive for ADA, six subjects seroconverted from negative at screening to positive after receipt of the study drug. There does not appear to be shared clinical findings among these six subjects to suggest a common syndrome attributable to *de novo* seroconversion from negative to positive for ADA following exposure to Eloctate (Section 3.1.1.1 (c)). In addition, five subjects tested positive for ADA prior to receipt of Eloctate. The significance of this finding is unclear. It is important to note however, that the assay used to determine ADA positivity has been developed by the sponsor for the specific purpose of conducting clinical trials in support of this BLA. The assay has not been replicated and validated in widespread use.

The available data submitted by the sponsor have also evaluated safety concerns particular to this Fc fusion product. Since Eloctate has a long half- life it should be dosed less frequently. However, dosing errors are possible especially because Eloctate is the first long acting FVIII product available on the US market and will therefore require a novel dosing schedule, unfamiliar to patients and providers in the hemophilia community. Should excessive amounts of the product be administered, the theoretical risk of thrombosis has been evaluated by the sponsor in the clinical safety database. A single study subject reported perianal venous thrombosis which was later thought to represent a rectal hemorrhoid (Section 3.1.1.1(d)). All adverse events related to dosing errors will be evaluated as described in the PVP.

While the prelicensure trials have evaluated many of the known safety concerns for Eloctate, there is limited information on the use of the product in PUPs, and on long-term use of the Eloctate in all populations for which the product would be indicated. The sponsor proposes a postmarketing study in PUPs to evaluate use of the product in this sub-population and estimates that a majority of study subjects will receive the product long-term in the planned Extension Trial.

5. RECOMMENDATIONS

At this time OBE agrees with the planned pharmacovigilance activities listed in the PVP. OBE recommends that the two ongoing postmarketing studies listed in the PVP be considered clinical PMCs requiring submission to FDA of interim reports at prespecified intervals and a final study report for each of the two studies. Similarly, OBE recommends that the planned PUPs study listed in the PVP be considered a clinical PMC, requiring submission to FDA of the study protocol and planned milestones as well as interim and final study reports at prespecified times.

Of note, on 12Feb2014, during the European Medicine Agency (EMA)-FDA-Health Canada (HC) Blood Cluster Meeting, the EMA reported on their ongoing evaluation of potency assays for FVIII and FIX products. There are currently two potency assays in widespread use for the evaluation of these products – the one-stage clotting assay and the chromogenic assay. The EMA commented that in their experience the chromogenic assay is more robust with the traditional factor products but that it was unclear which assay would be used for newer FVIII products such as Eloctate. Biogen Idec has submitted applications for licensure for Eloctate to HC as well as FDA but not EMA. HC and FDA concurred that the question should be clarified prior to the licensure of Eloctate. The decision regarding the potency assay recommended for Eloctate will therefore be discussed prior to the action due date of this submission. In general, OBE agrees with the plan to clarify the potency assay of choice for Eloctate prior to licensure.