



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

MEMORANDUM

Date: 9 October 2014

From: Wambui Chege, MD
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Re: STN 125555\0

Through: Christopher Jankosky, MD, MPH
Branch Chief, Pharmacovigilance Branch

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Product: Nuwiq[®] (simoctocog alfa), [Antihemophilic Factor (Recombinant) plasma/albumin free]

Subject: Original Biologics License Application
Action Due Date 5Jun2015

Sponsor: Octapharma

1. INTRODUCTION

On 5Jun2014, Octapharma submitted an original Biologics License Application (BLA, 125555/0) to the Food and Drug Administration (FDA) for Nuwq (simoctocog alfa) – a B-domain deleted recombinant Factor VIII (BDDrFVIII) product synthesized in Human Embryonic Kidney (HEK) cells and without the use of human serum or other animal-derived components.

The sponsor's proposed indication is for the control and prevention of bleeding episodes (including during and after surgery) in adults and children with Hemophilia A. Nuwq will be supplied as a white sterile lyophilized powder for reconstitution with a pre-filled syringe of 2.5 mL sterile water for injection. The product will be available in single-use vials containing 250, 500, 1000 or 2000 International Units (IU).

Nuwq was first approved in the European Union (EU) on 22Jul2014 and was subsequently approved in Canada and Australia on 23Oct2014 and 5Nov2014, respectively.¹ The international postmarketing experience with Nuwq is reviewed in detail in section 3.2.1 below.

1.1 BDDrFVIII products – the newest subset of the class

The earliest recombinant FVIII (rFVIII) products were manufactured from the *in vitro* transcription and translation of the entire FVIII gene, resulting in a full-length FVIII molecule which is comprised of three major domains. The B-domain is a large central region of the FVIII molecule which 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.² In BDDrFVIII products, the B-domain is

(b) (4) Deletion of the B-domain reduces the size of the FVIII molecule 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.³

There are currently three BDDrFVIII products marketed in the US. The first approved BDDrFVIII product – ReFacto, was produced by Wyeth and licensed by the FDA on 6Mar2000. Wyeth improved on ReFacto 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 and was approved by the FDA on 21Feb2008. 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. A second BDDrFVIII product produced by Novo Nordisk named NovoEight was licensed by the FDA on 15Oct2013. Biogen Idec's product Eloctate was the third BDDrFVIII product approved by FDA on 6Jun2014. Eloctate is comprised of a BDDrFVIII molecule covalently linked to the Fc domain of human immunoglobulin which confers a longer half-life on the product.

1.2 Known Safety Concerns and Historical Evolution to BDDrFVIII products

Known safety concerns for the class of FVIII products – particularly the risk of transmission of infectious agents and the development of antibodies to the product – have led to changes in the manufacture of these products over time, culminating in the development of BDDrFVIII products, the newest subset in the class. This evolution in the manufacture of FVIII products is summarized in Table 1 below and the safety concerns of infectivity and immunogenicity are described in sections 1.2.1 and 1.2.2 below respectively.

Table 1. Summary Timeline of Historical Evolution to BDDrFVIII products^{2,3,4,5}

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. ⁴
1990s	Full-length recombinant FVIII products become commercially available and are a popular alternative to plasma-derived concentrates due to the reduced risk of viral transmission.
2000	The first BDDrFVIII product ReFacto is licensed by FDA. Elimination of the B-domain results in greater ease of manufacturing and the production of a smaller stable molecule that is as effective in coagulation as full-length products.
2008	Xyntha – a BDDrFVIII albumin-free cell culture product is licensed by FDA and replaces ReFacto in the US market.
2013	FDA licenses NovoEight – a BDDrFVIII product manufactured by NovoNordisk
2014	Biogen Idec’s product Eloctate is approved by FDA and becomes the third BDDrFVIII product marketed in the US

1.2.1 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 1).

As with other recombinant products, BDDrFVIII products seek to offer a lower risk of transmission of viral pathogens than plasma-derived products. The three BDDrFVIII products currently licensed in the US are all produced in the absence of human and other animal derived-components to reduce the risk of transmission of infectious pathogens. Similarly, Nuwiq is manufactured without the use of human serum or other animal-derived components.

1.2.2 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, both NovoNordisk and Biogen Idec have provided information regarding immunogenicity in support of their respective BLAs for NovoEight and Eloctate. These findings are summarized in sections 1.2.2.1 and 1.2.2.2 below. Safety information submitted by Octapharma in support of the Nuwiq BLA is reviewed separately in section 3 below.

1.2.2.1 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.⁶ 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.⁷

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.⁸ 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.

Similarly, safety related data submitted in support of licensure for Eloctate was notable for a single study subject who developed a single low titer inhibitor test which was negative on repeat testing and the patient had no clinical evidence of bleeding.⁹

1.2.2.2 Antibodies to non-human proteins

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.¹⁰

Unlike both Xyntha and NovoEight which are produced in CHO cells, Eloctate and Nuwiq are both 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 evaluation of BDDrFVIII products for known safety concerns for the class of FVIII products, such as risk of infection and immunogenicity, indicate that the safety profile of BDDrFVIII products is comparable to or better than that of other products in the class.

1.3 Additional Classification of Recombinant FVIII products

As described in section 1.2 above, known safety concerns for the class of FVIII products have led to the development of rFVIII products, and more recently BDDrFVIII products. rFVIII products can therefore be classified as either full-length or BDDrFVIII products. rFVIII products can also be classified according to changes in manufacturing which are intended to reduce the risk of transmission of viral pathogens and the risk of development of antibodies to foreign proteins. Over time each successive generation of rFVIII products has aimed to further reduce these risks as described in Table 2 below. For example, of the three currently approved BDDrFVIII products, two are 3rd generation products – Xyntha and NovoEight, as they are produced in CHO cells, a hamster cell line, and in the absence of any additional human or animal proteins. By contrast, Eloctate is produced in HEK cells, a human cell line, and in the absence of human or animal proteins. Eloctate was therefore the first 4th generation BDDrFVIII product approved by FDA. Should Nuwiq be approved, it would be the second 4th generation BDDrFVIII product licensed by FDA.

Table 2. Classification of Generations of rFVIII Products According to Manufacturing Practice

Manufacturing practice	Generation of rFVIII products			
	1 st	2 nd	3 rd	4 th
Produced in Hamster or non-Human cell line?	Yes	Yes	Yes	No
Use cell culture media containing human and/or animal proteins?	Yes	Yes	No	No
Use human albumin as a stabilizer in the final formulation?	Yes	No	No	No

2. OBJECTIVES

This memorandum follows a request from the FDA’s Office of Blood Research and Review (OBRR) to review the available safety related information for Nuwiq in the context of the sponsor’s proposed postmarketing safety surveillance. In addition to the Pharmacovigilance Plan (PVP) submitted by the sponsor as part of the Risk Management Plan (RMP), study reports of prelicensure clinical trials, summary safety reports and the protocols for planned future studies were also reviewed. A search of Pubmed.gov and Clinicaltrials.gov for published literature with safety related endpoints using the search terms “simoctocog” or “Nuwiq” revealed no additional documents to review.

3. PHARMACOVIGILANCE PLAN REVIEW

3.1 Clinical Safety Database

The overall clinical development program submitted by Octapharma for Nuwiq consists of a total of 10 clinical trials (Table 3). Of these 10 trials, 6 have been completed in the prelicensure phase and 4 will be continued in the postlicensure phase. The 6 prelicensure studies included in the clinical safety database have been reviewed in detail and are described in Table 3 below. Final study reports have been received for all 6 trials, and safety-related study results are reviewed in section 3.1.2 below.

Of note, Octapharma is also currently conducting an eleventh trial GENA-21 – a study to investigate the efficacy and safety of a personalized prophylaxis regimen in adult PTPs with severe hemophilia A in Europe. A related trial GENA-21b, expands the protocol to permit patient recruitment worldwide.¹¹ Data from these studies of personalized prophylaxis have not been included in the current BLA, as the sponsor is currently seeking the indication of regularly scheduled (rather than personalized) prophylaxis of bleeding.¹²

Table 3. Prelicensure Trials conducted for Nuwiq

Study ID/ Period	Study Title	Study Design	Study Population	Study Status
GENA-01 “Kogenate comparison trial” 27-May-2010 to 18-Sep-2012	Clinical study to investigate PK, efficacy, safety and immunogenicity of Nuwiq in PTPs with severe HA	Phase II Prospective, randomized, controlled, open-label, cross over, international, multicentre	PTPs with severe HA	Complete, Study report available
GENA-11 (extension of GENA-01) 14-May-2012 to 30-Aug-2012	Clinical study to investigate the long-term efficacy, safety, and immunogenicity of Nuwiq in PTPs with severe HA	Phase IIIb Prospective, open-label, uncontrolled, international, multi-center	PTPs with severe HA	Terminated, Study report available

GENA-03 “Pediatric trial” 27-Dec-2010 to 06-Nov-2012	Prospective clinical study in children with severe HA to investigate clinical efficacy, immunogenicity, PK and safety of Nuwiq	Phase III Prospective, international, multicentre, open-label	PTPs with severe HA	Complete, Study report available
GENA-08 “Adolescent and adult trial” 22-Jun-2010 to 31-Jan-2012	Clinical study to investigate the efficacy, safety, and immunogenicity of Nuwiq, in PTPs ≥ 12 yo with severe HA	Phase III Prospective, international, multicentre, open-label, non-controlled	PTPs with severe HA	Complete, Study report available
GENA-09 “Adult trial” 16-Mar-2009 to 26-May-2010	Clinical study to investigate the PK, efficacy, safety and immunogenicity of Nuwiq in PTPs with severe HA	Phase III Prospective, single-center, open-label	PTPs with severe HA	Complete, Study report available
GENA-04 (extension of GENA-09) 21-Nov-2009 to 28-Jul-2011	Clinical study to investigate the long-term safety and efficacy of Nuwiq in PTPs with severe HA	Phase IIIb Prospective, single-center, open-label	PTPs with severe HA	Complete, Study report available

PK=Pharmacokinetics, HA=Hemophilia A, PTPs=Previously Treated Patients

3.1.1 Prelicensure Clinical Trial Safety Information

3.1.1.1 Overview of Completed Trials

At total of 6 completed trials are included in the clinical safety database for Nuwiq (Table 3 above). However data from GENA-11, the extension study of GENA-01 which was terminated early, are not included by the sponsor in the overall safety data submitted in support of this BLA. GENA-11 was initiated on 14May2012 to assess the long-term safety and efficacy of on-demand treatment with Nuwiq. The study was terminated prematurely because only 3 of the eligible patients in GENA-01 enrolled in the extension study and all 3 withdrew their consent within 3 months. An abbreviated study report for GENA-11 has been provided by the sponsor. The sponsor reports no AEs in GENA-11 and that the study was not terminated due to any safety-related issues.

The overall safety data submitted by the sponsor is derived from the other 5 completed studies in the clinical safety database. In total, 135 unique male patients with severe hemophilia A were enrolled in these clinical trials. Across the 5 completed studies, patients received a total of 32,650,787 IU of Nuwiq via 16,134 infusions over 15,950 exposure days (EDs). Safety-related endpoints for all 5 studies included physical examination including vital signs, laboratory assessments, immunogenicity and tolerability. In addition, given that some proportion of patients receive Nuwiq via central venous access devices, catheter related complications following administration of clotting factor, such as thromboembolism are of particular importance. Safety-related results from these studies is summarized in Table 4 below. Of note, GENA-08 was intended to be distinct from GENA-09 in that planned enrollment in the former included both adolescents and adults (aged 12 to 65 years), whereas the latter was intended exclusively for adults (≥ 18 years). However, due to difficulty in recruiting adolescents, study subjects in both trials are adults aged 18 and older resulting in similar study populations for the two trials (Table 3 above).

Table 4. Safety-related Results from the Clinical Safety Database for Nuwig

	GENA-01 “Kogenate Comparison trial” N=22	GENA-03 “Pediatric trial” N=59	GENA-08 “Adolescents and Adults” N=32	GENA-09 “Adults trial” N=22	GENA-04 (Extension of GENA-09) N=18
Age (years)					
Mean±SD	39.6±14.06	6.1±2.97	37.3±13.6	24.5±9.77	25.83±10.55
Range	12–65	2–12	18–75	18–62	18–62
Height (cm)					
Mean±SD	174.0±9.41	122.5±19.78	178.4±7.9	177.5±6.58	N/A
Range	154–188	82–173	158–192	166–191	N/A
Weight (kg)					
Mean±SD	72.7±15.55	26.7±12.33	82.5±18.0	69.0±13.82	73.0±14.37
Range	46–105	8–73	47–127	50–105	55–110
Race (%)					
White	81.8	100	90.6	100	100
Asian	0	0	9.4	0	0
Black	13.6	0	0	0	0
Native American	4.5	0	0	0	0
Safety-related Results					
Immunogenicity	Transient inhibitor present in 1 patient at screening, disappeared during study, no clinical sequelae	No inhibitors. Low titer non-inhibitory antibody in 2 patients, no clinical sequelae	No inhibitors	No inhibitors	No inhibitors
Adverse Events	3 SAEs in 2 patients – Depression suicidal, Hepatic encephalopathy, Hepatic cirrhosis. No deaths, no TEEs.	7 SAEs in 5 patients – Hemarthrosis, Port-a-cath Infection, Acute tonsillitis, URI, LRI, 2 reports of Head Injury. No deaths, no TEEs.	2 SAEs in 2 patients – Traumatic fracture, Status epilepticus resulting in death. No TEEs.	No SAEs. No deaths, no TEEs.	No SAEs. No deaths, no TEEs.

SD=Standard deviation, SAE=Serious adverse event, URI=Upper Respiratory Tract Infection, LRI=Lower Respiratory Tract Infection, TEEs=Thromboembolic events

A single death was reported in the clinical safety database for Nuwig. In study GENA-08 patient (b) (6) was a 26 yo Caucasian man with a history of severe hemophilia A and epilepsy diagnosed in 1997 and treated with oxycarbazepin, 300 mg twice a day. He received Nuwig from (b) (6) through (b) (6) for a total exposure of 140,370 IU, 2608.3 IU/kg and 76 EDs. On (b) (6) 48 days after his

last documented Nuwiq infusion, the patient was found dead following an episode of status epilepticus. The cause of death was documented as acute respiratory and cardiovascular failure.

3.1.1.2 Pooled Analyses of Completed Trials

In addition to providing the final study reports for all completed trials in the clinical safety database, the sponsor has also provided analyses of pooled data from completed trials for two outcomes of interest – surgery and inhibitors. These analyses have been reviewed in detail and are summarized in sections 3.1.1.2 (a) and (b) below.

3.1.1.2 (a) – Pooled Analysis of Surgical Prophylaxis

In this analysis, the sponsor provides statistical evaluation of the efficacy of Nuwiq when used for surgical prophylaxis using data pooled from the 5 studies included in the clinical safety database (Table 4). Across these 5 studies, 19 patients underwent a total of 34 surgeries and surgical prophylaxis with Nuwiq rated as either excellent or good in 94% (95% CI; 80.3-99.3%) of surgeries. No aggregate analyses of safety-related endpoints was reported.

3.1.1.2 (b) – Pooled Analysis of Incidence of Inhibitors

The sponsor performed statistical analyses of the incidence of inhibitors in patients enrolled in 4 of the 5 studies included in the clinical safety database – GENA-01, GENA-03, GENA-08 and GENA-09. The extension study GENA-04 was excluded from this analysis. The sponsor reports an incidence of inhibitors of 0/135 (95% CI; 0.00-0.03) among all patients and 0/127 (95% CI; 0.00-0.03) among patients with ≥ 50 EDs.

3.2 Pharmacovigilance Plan

The Pharmacovigilance Plan (PVP) for Nuwiq has been reviewed in detail and is summarized in Table 5 below.

Table 5. Summary of Pharmacovigilance Plan for Nuwiq

Safety Concern	Planned Activity
Important Identified Risks	
Inhibitor development	GENA-05, GENA-13, GENA-15, GENA-99 EUHASS Routine Pharmacovigilance
Important Potential Risks	
Hypersensitivity including anaphylaxis	GENA-13, GENA-99 EUHASS Routine Pharmacovigilance
Thromboembolic events	GENA-99 EUHASS Routine Pharmacovigilance
Medication errors including in home setting	GENA-99 EUHASS Routine Pharmacovigilance
Missing Information	
Safety in Previously Untreated Patients (PUPs)	GENA-05 Routine Pharmacovigilance
Use in children <2yo	GENA-05, GENA-99 Routine Pharmacovigilance
Safety in patients with mild or moderate hemophilia A and patients with high risk	Routine Pharmacovigilance

gene mutations	
Safety in elderly patients and patients of different ethnic origins	GENA-99 Routine Pharmacovigilance
Safety in pregnant or breastfeeding women, patients with renal or hepatic impairment and patients with HIV or other infections	Routine Pharmacovigilance
Immune tolerance induction (ITI)	GENA-05 Routine Pharmacovigilance

A total of 4 studies are planned in the postmarketing phase and are listed in the PVP. Protocols for all 4 studies have been reviewed in detail and are summarized in section 3.2.1 below. In addition to routine pharmacovigilance and the planned postmarketing studies, the sponsor also plans to engage with the European Haemophilia Safety Surveillance (EUHASS) program. EUHASS is a pharmacovigilance program which was launched on 1Oct2008 to monitor the safety of treatments for people with inherited bleeding disorders in Europe. Hemophilia treatment centers across Europe report adverse events directly to the EUHASS website. Participating centers also provide data on the number of patients registered with them and the clotting factor concentrates used to treat them. EUHASS produces brief, quarterly reports of adverse events as well as a more detailed annual report, with analysis of event rates according to diagnosis, treatment status and clotting factor concentrate. Reports are distributed to the participating centers, to the pharmaceutical companies co-funding the project, to European patient groups, to regulatory agencies and to healthcare professionals providing care to patients with bleeding disorders in Europe.¹³ Octapharma proposes reporting relevant information from EUHASS product-specific reports in the PSURs and PBRERs submitted to FDA following licensure of Nuwiq.

3.2.1 International Postmarketing Experience and Postmarketing Studies Listed in the PVP

Nuwiq was first approved in the EU on 22Jul2014 and was subsequently approved in Canada and Australia. The sponsor has provided a 120 day safety report detailing the current international postmarketing experience with Nuwiq including interim results from the postmarketing studies listed in the current PVP (Table 5 above).¹ In the 120 day safety report, Octapharma reports receiving no spontaneous AE reports for Nuwiq as of 30Nov2014. Interim results from the PVP postmarketing studies are summarized in Table 6 below.

Of note, a total of 8 serious AE reports of inhibitor development were received from study GENA-05. Given that GENA-05 is a PUPs study and that PUPs are thought to be at higher risk for development of inhibitors than PTPs,¹⁴ reports of inhibitor development in this particular study population can be expected. GENA-15 is an extension of GENA-05 and is therefore comprised of a similar study population. The fact that reports of inhibitors have been received in GENA-05 but not GENA-15 may be a reflection of the relatively small number of study subjects in GENA-15, selection bias where healthier patients may be more likely to enroll in the extension study or multiple other factors. No AE reports have been received from studies GENA-13 or GENA-21. Study GENA-99 will be launched in the first quarter of 2015.

Table 6. Summary of Postmarketing Studies for Nuwiq

Study ID/ Period	Study Title	Study Design	Study population	Goal recruitment (n)	Study Status and Milestones
GENA-05 “PUPs trial” 15-Mar-2013 to Q4 2018	Immunogenicity, efficacy and safety of treatment with Nuwiq in PUPs with severe HA	Phase III Prospective, international, multicentre, open-label, non- controlled	PUPs with severe HA	n = 100; n=50 as of 30Nov2014	Ongoing. Interim analyses after 30 patients start treatment and after 50 patients achieve ≥ 50 Exposure Days (ED). Final Report due 2019.
GENA-15 (extension of GENA-05 “PUPs trial”) 19-Mar-2014 to Q1 2016	Extension Study for Patients who completed GENA-05 (NuProtect) – to Investigate Immunogenicity, Efficacy and Safety of Treatment with Nuwiq	Phase IIIb Prospective, multicentre, multinational, open-label, non- controlled	PTPs with severe HA	n \leq 100; n=6 as of 30Nov2014	Ongoing. Final report due 2016.
GENA-13 (extension of GENA-03 “Pediatric trial”) 25-Oct-2011 to Q3 2015	Clinical study in previously treated children with severe HA to investigate the long-term immunogenicity, tolerability and efficacy of Nuwiq	Phase IIIb Prospective, international, multicentre, open-label	PTPs with severe HA	n=49 as of 30Nov2014	Ongoing. Final report due 2016.
GENA-99 “Long-term Observational study”	Observational study of the long-term immunogenicity, safety, and efficacy of Nuwiq in routine clinical practice	Phase IV, Prospective, multinational, non- interventional postauthorization study	PTPs	n=200 of whom: 100 will have severe HA, 60 will be < 12 yo, 10 will be 14–18 yo and $\leq 25\%$ can be post- ITI	Interim report 2 years after approval. Final report due 2020.

4. INTEGRATED RISK ASSESSMENT

Review of the available safety data in the BLA for Nuwiq is notable for several limitations of the clinical safety database. These are reviewed in the context of the proposed postmarketing PVP in sections 4.1 to 4.4 below.

4.1 Predominance of male gender

A total of 135 unique patients have been evaluated in the clinical development program for Nuwiq (Table 4 above). All patients 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 should it be approved.

4.2 Limited experience in PUPs

All study subjects in the prelicensure clinical safety database are PTPs. Following licensure in the EU, Canada and Australia, the sponsor has provided some international postmarketing data regarding use of Nuwiq in PUPs (Table 6). However, given that Nuwiq has been licensed in these international markets for less than 12 months, and that the proposed PUPs postmarketing studies have only recently been launched, data provided by the sponsor regarding use of Nuwiq in PUPs is limited (Table 6). It is important to note however that this approach – use of PTPs as study subjects in prelicensure studies, followed by postlicensure evaluation of PUPs – is consistent with recommendations from the European Medicines Agency (EMA) and the International Society on Thrombosis and Hemostasis (ISTH). PTPs, by virtue of not having developed an inhibitor, are generally considered to be tolerant of FVIII 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.¹⁵ 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.¹⁶ The sponsor's limited experience in PUPs at this stage, and the plan to further evaluate use of Nuwiq in PUPs in the postmarketing phase is therefore consistent with current expert guidelines.

4.3 Relatively low risk population for development of 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, PUPs and severe disease requiring intense replacement therapy.¹⁴ Although all patients in the prelicensure clinical safety database are severe hemophiliacs, PUPs were excluded, subjects with a history of inhibitors were also excluded and the majority of patients reported their ethnicity as white (Table 4). The sponsor has provided some postmarketing information regarding inhibitor development in PUPs (section 3.2.1) and plans additional evaluation of risk factors for immunogenicity in several postmarketing studies (Table 6). At this time however, postmarketing data is limited due to the short period since international licensure and the early stage of the postmarketing studies. Thus, with regard to the development of FVIII inhibitors, the available data result primarily from the prelicensure clinical safety database, and the risk profile of this population is not fully representative of the wider target population in which this product will eventually be used. Of note however, as the postmarketing experience with Nuwiq evolves, an overall study population more representative of the target population should emerge, providing a more robust understanding of the risk of inhibitor development with Nuwiq over time.

4.4 Limited experience with specific age populations

The age of study subjects in the clinical safety database ranges from 2 to 75 years of age (Table 4 above). However, the mean age of pediatric subjects is about 6 years old and the mean age of adult subjects ranges from 25 to 40 years of age. There is therefore limited information on use of Nuwiq in very young children and the elderly. In addition, despite the proposed inclusion criteria in GENA-08, no adolescent patients were recruited in the trial and there is therefore no information regarding use of Nuwiq in individuals aged 12 to 18 years (Table 4 above). Of note, however, experience in these 3 populations – young children, the elderly and adolescents – may be obtained in the postmarketing phase through the

proposed studies listed in the PVP, GENA-05 (“PUPs trial”), GENA-15 (extension of “PUPs trial”), GENA-13 (extension of “Pediatric trial”) and GENA-99 (“Long-term Observational trial”).

5. RECOMMENDATIONS

At this time OBE agrees with the postmarketing surveillance and post-approval studies proposed by the sponsor in the PVP. The 4 proposed postmarketing commitment studies (PMCs) listed in the PVP may prove useful, particularly with regard to current areas of limited information regarding use of the product in specific populations. These studies may be considered clinical PMCs, meaning that should the product be licensed, the studies can be listed as formal commitments on the approval letter and that the sponsor commits to meeting the prespecified milestones including prompt submission of interim and final study reports to FDA as described in the study timeline. At this time, the available safety data do not substantiate a need for a post-marketing requirement (PMR) study or a Risk Evaluation and Mitigation Strategy (REMS).

¹ Octapharma. Periodic Safety Update Report. 22-Dec-2014 120day Safety Report for 04-Aug-2014 to 30-Nov-2014 eCTD 125555/0.15

² 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.

³ 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

⁴ National Hemophilia Foundation, Blood and Product Safety, HIV/AIDS. Available at: <http://www.hemophilia.org>

⁵ Hoots WK and Shapiro AD. Treatment of Hemophilia. *UpToDate* 2012. Available at <http://www.uptodate.com/contents/treatment-of-hemophilia>.

⁶ 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)

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⁸ NovoNordisk. Complete Study Report Pivotal trial NN7008-3545 08Feb 2012. eCTD 125466/0

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