Summary Basis for Regulatory Action

Date	September 4, 2015
From	Andrey Sarafanov, PhD, Committee Chair
Subject	Summary Basis for Regulatory Action
BLA STN	125555/0
Applicant	Octapharma Pharmazeutika Produktionsges.m.b.H.
Date of Submission	June 5, 2014
PDUFA Goal Date	September 4, 2015
Trade Name / Established Name	NUWIQ/ Antihemophilic Factor (Recombinant), rAHF
Dosage Form	Lyophilized powder with nominal potencies: 250 IU, 500 IU, 1000 IU or 2000 IU per vial
Proposed Indication(s)	1) On-demand treatment and control of bleeding episodes in adult and pediatric patients, (2) Perioperative management of bleeding in adult and pediatric patients, and (3) Routine prophylaxis to reduce the frequency of bleeding episodes in patients with Hemophilia A. NUWIQ is not indicated for the treatment of von Willebrand Disease.
Recommended Action	Approval
Signatory Authority Action	Jay Epstein, MD_____ *Offices Signatory Authority* *I concur with the summary review* ☐ *I concur with the summary review and include a separate review or addendum to add further analysis* ☐ *I do not concur with the summary review and include a separate review or addendum* Mary A. Malarkey_____ *Offices Signatory Authority* ☐ *I concur with the summary review* ☐ *I concur with the summary review and include a separate review or addendum to add further analysis* ☐ *I do not concur with the summary review and include a separate review or addendum*

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1. Introduction

Octapharma Pharmazeutika Produktionsges.m.b.H. (Octapharma) has submitted an original biologics license application (BLA) to seek U.S. licensure for Antihemophilic Factor (Recombinant). The commercial product is a lyophilized powder in a crimp-sealed, stoppered, glass vial, available in nominal potencies of 250, 500, 1000, or 2000 international units (IU). The product is reconstituted with sterile water for injection provided in a pre-filled syringe. The proprietary name of the product to be marketed in the U.S. is NUWIQ.

NUWIQ is indicated for adults and children with Hemophilia A (congenital deficiency in Coagulation Factor VIII (FVIII)]) for: (1) On-demand treatment and control of bleeding episodes in adult and pediatric patients, (2) Perioperative management of bleeding in adult and pediatric patients , and (3) Routine prophylaxis to reduce the frequency of bleeding episodes. NUWIQ is not indicated for the treatment of von Willebrand Disease.

2. Background

Hemophilia A is a rare, hereditary, hematologic disorder caused by deficiency or dysfunction of FVIII (historically referred to as Antihemophilic Factor), resulting in bleeding secondary to abnormal clot formation. Because the FVIII gene is located on the X-chromosome, Hemophilia A has an X-linked, recessive inheritance pattern, affecting one in 5,000 male births. Women who are carriers of Hemophilia A may also have levels of FVIII that are low enough to be clinically significant. To promote clotting, treatment includes replacement of the deficient FVIII by intravenous administration of a purified FVIII concentrate. Both plasma derived and recombinant DNA derived FVIII concentrates (pdFVIII and rFVIII, respectively) are commercially available. In recent years, treatment regimens have shifted from on-demand treatment of bleeding episodes to routine prophylaxis because of an observed improvement in long-term clinical outcome.

NUWIQ is a recombinant analogue of human FVIII, which is a heterodimer, composed of an N-terminal heavy chain and a C-terminal light chain. The B-domain, of approximately 900 amino acids, located at the C-terminus of the heavy chain, is genetically deleted; thus NUWIQ is a B-domain deleted rFVIII (BDD-rFVIII) protein. The B-domain (b) (4)

Because the BDD-rFVIII of NUWIQ is expressed in human cells (HEK293), it has post-translational modifications more similar to those in pdFVIII compared to the products with recombinant FVIII expressed in animal cells. In particular, the carbohydrate moiety of proteins expressed by human cells contains N-acetyl neuraminic acid (a sialic acid), rather than the N-glycolyl neuraminic acid present in the carbohydrate of proteins from animal cells.

Clinical trials that provided the evidence for safety and efficacy of NUWIQ were conducted under IND 13722. To support licensure for the proposed indications, the clinical development program included: (1) a pharmacokinetic study with secondary safety and efficacy outcomes in adults, (2) an efficacy study with secondary PK outcomes in adults, and (3) an efficacy study in children 2-5

and 6-12 years of age to support the indication for use in children. All of these studies enrolled subjects who were previously treated with a FVIII product (≥150 exposure days in subjects ≥12 years of age, and ≥50 exposure days in subjects <12 years of age). Two additional non-IND trials were carried out at a single foreign center in subjects with chronically undertreated disease and more severe clinical sequelae.

NUWIQ is currently licensed in 33 European countries, Canada and Australia.

During the review of the BLA, a number of significant issues were identified. These issues were related to Chemistry, Manufacturing and Controls, and were deficiencies in validation of the manufacturing processes and in the analytical methodology used to verify the product quality and stability. Upon further communication with Octapharma, these issues were resolved.

3. Chemistry, Manufacturing and Controls (CMC)

a) Product Quality

Source Materials

The source materials for the manufacture of BDD-rFVIII involve reagents and a starting cell bank. For generation of the cell bank, a commercially available human embryonic kidney 293F (HEK 293F) cell line was used. These cells were genetically modified to carry the gene coding for BDD-rFVIII, and were tested for the absence of viruses and mycoplasma. This was followed by generation of the master cell bank (MSB), from which the working cell bank (WCB) was produced. The cell banks were extensively characterized for the BDD-rFVIII gene copy number, absence of adventitious agents, viability, and genetic stability. All other source materials used for BDD-rFVIII manufacture are either compendial (USP, Ph. Eur.) or in-house specified and do not contain animal- or human-derived materials that could potentially introduce contamination with adventitious agents. All source materials are purchased from certified vendors and tested in-house for identity.

Manufacturing Process

The manufacturing process of BDD-rFVIII includes cell culturing, collecting a harvest with expressed BDD-rFVIII, and purification of the BDD-rFVIII. Purification consists of a series of multimodal chromatography steps (b) (4) chromatography), two dedicated virus clearance steps (solvent-detergent treatment and nanofiltration), and formulation with excipients (USP, Ph. Eur.) to adjust its composition to that of the drug substance (DS). The DS (b) (4) the drug product (DP) powder. The solvent, sterile water for injection (WFI), is manufactured from (b) (4) , and is supplied in pre-filled syringes. The final DP, consisting of the powder and solvent components, is packed, labeled and released for marketing.

Development of the Manufacturing Process

Octapharma made a number of changes during the development of the manufacturing process. In particular, this included optimization of conditions of (b) (4) . Modifications during the pharmaceutical development included: (b) (4)

To demonstrate comparability of the DP lots manufactured during the process development,

Octapharma performed studies, which included extensive physico-chemical characterization of the lots and their nonclinical and clinical testing. These studies demonstrated that the manufacturing changes did not affect the safety and efficacy of the DP. To demonstrate compatibility of the DP with the container and injection device, Octapharma compared the FVIII activity of samples that had been passed through the injection set to those taken immediately after reconstitution.

Validation of the Manufacturing Process

Validation of the manufacturing process included manufacture of (b) (4) process performance qualification DP lots covering all product strengths (250, 500, 1000, and 2000 IU/vial), and minimum and maximum lot sizes (in 2014). Octapharma also evaluated the process using an additional (b) (4) DP lots manufactured in 2008-2012. Validation of the cell cultivation and BDD-rFVIII purification process included validation of hold-times for (b) (4), solvent-detergent treatment, and chromatography column life-times (number of process cycles). Validation of the process downstream of the DS included validation of (b) (4) and transportation of the DP from OAB Stockholm Sweden to Octapharma (b) (4). Process validation of the DP solvent, WFI, included manufacture and testing of consecutive lots of WFI pre-filled syringes. All test results were within respective specifications which supported consistency of the manufacturing processes.

Process Critical Steps

Process critical steps include (b) (4) Each of these steps is controlled by multiple *Process Control Parameters*. In particular, for the (b) (4) process these parameters are (b) (4)

Quality Attributes of the Drug Product

The product quality attributes were determined during the manufacturing process validation. This included an assessment of the impact of the product's physicochemical characteristics on its efficacy, pharmacokinetics and immunogenicity. These product attributes were defined to be FVIII Activity, (b) (4), Water Content, Excipient Concentration, (b) (4), and Sterility/Microbiology.

Release Specifications of the Drug Product

The product quality attributes were listed in the product release specifications. To control the specification parameters, suitable analytical methods were established. These methods, either described under USP (Ph. Eur) or developed in-house, were validated for suitability for the intended use. An acceptable reference standard qualification and a maintenance program were established. The most critical specification parameters of the lyophilized DP and respective analytical methods are listed in Table 1.

Table 1. Most important specifications parameters of the lyophilized Drug Product.

Test	Method	Acceptance Criteria
Appearance:	(b) (4)	A white cake. Possibly a small amount of white powder
(b) (4) :	(b) (4)	(b) (4)
(b) (4) :	(b) (4)	(b) (4)
Solubility at 20-25°C, time:	(b) (4).	(b) (4)
Visual inspection of solution:	(b) (4).	Clear, colorless solution, practically free from visible particles
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Water:	(b) (4)	(b) (4)
Sterility:	(b) (4)	Approved
Endotoxin:	(b) (4)	(b) (4)
Potency:	One-Stage (clot)	(b) (4) (250 IU) (b) (4) (500 IU) (b) (4) (1000 IU) (b) (4) (2000 IU) Should be within (b) (4) of the labeled value throughout the product shelf-life under the licensed storage conditions
(b) (4) s	(b) (4)	(b) (4)
Total protein:	(b) (4)	(b) (4) (250 IU) (b) (4) (500 IU) (b) (4) (1000 IU) (b) (4) (2000 IU)
Specific FVIII:C activity:	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Storage and Expiry Date: Period of validity from the date of manufacturing:		24 months at +2 to +8°C, protected from light - from date of manufacture. The product may be kept at room temperature (up to 25°C) for a single period not exceeding 3 months. After storage at room temperature, the product must be used or discarded

Other (non-listed in the Table 1) parameters include limits and respective methods for the following excipients: sodium, calcium, chloride, citrate, sucrose, poloxamer 188 and arginine. During review, substantial issues in validation of a method to control the (b) (4) parameter by (b) (4) were identified. The most critical issues were resolved. Remaining method validation issues were considered not to affect the product's safety and efficacy, and Octapharma committed to resolve them after the BLA approval (Section 11.d).

For the DP solvent (WFI), the specification parameters include (b) (4) Endotoxin and Sterility. The shelf-life of the WFI container is five years when stored at 2-8 C at ambient humidity.

The DP (powder and WFI) specification limits are consistent with current guidelines including those of the U.S. and European Pharmacopoeias, and with specifications for other rFVIII products approved by the FDA in recent years. The analytical methodologies were adequate for process quality control throughout the NUWIQ manufacture, final release and stability monitoring.

Analytical Characterization of the Drug Product

The (b) (4) drug product lots used in process validation and clinical studies were extensively characterized including (b) (4) This characterization of BDD-rFVIII confirmed the similarity of its structural and functional properties to those of pdFVIII.

Characterization of Impurities in the Drug Product

Removal of impurities was characterized using process validation lots of (b) (4) DP. *Product-Related Impurities* were defined as BDD-rFVIII molecular variants with properties that are different from those of the desired product, in particular, (b) (4) *Process-Related Impurities* are potential adventitious agents, residual host cell DNA, (b) (4) residual host cell proteins and components derived from the cell culture medium (b) (4). Additional impurities include (b) (4) endotoxin, bioburden and leachables. In particular, leachables were evaluated for the containe (b) (4) (Section 3.2.S.6).

The potential of contamination with non-viral *Adventitious Agents* (bacteria, fungi, and mycoplasma), is controlled through the use of cleaning/sanitization procedures, in-process controls (Bioburden) and (b) (4). The potential of contamination with non-viral adventitious agents is further reduced by controlling the DP for Endotoxin and Sterility. The potential contamination by adventitious viruses and transmissible spongiform encephalopathy (TSE) agents is minimized because, except for the cell line, there are no materials of human or animal origin used in the manufacturing process. Octapharma tests the Master Cell Bank according to the International Conference on Harmonization (ICH) Q5A(R1), and routinely tests cell cultures used in the manufacturing process, for adventitious viruses.

The potential risk of viral contamination of NUWIQ is further mitigated through the use of two dedicated viral clearance steps: Solvent/Detergent treatment (b) (4) and (b) (4) 20N nanofiltration. Octapharma evaluated these steps in scale-down studies with selected model viruses having a wide range of physico-chemical properties. (b) (4) The scale-down studies demonstrated the ability of the manufacturing process to reduce the potential viral contamination. Overall viral log reduction factors were: (b) (4).

In conclusion, the manufacturing process was found to provide sufficient purification of NUWIQ. The specifications limits for major impurities in the (b) (4) DP are established.

Container/Closure System

The 8 mL vials are manufactured from type (b) (4) glass (supplier - (b) (4), closed with (b) (4) stoppers (b) (4) (supplier - (b) (4)

(b) (4) and sealed with aluminum flip-off caps (supplier - (b) (4) The closed container was validated for integrity and absence of any negative effect on product quality and stability during the shelf-life. The solvent (WFI) is marketed in a pre-filled syringe, composed of (b) (4) glass barrel, (b) (4) plunger, and closure system. Its suitability for the intended purpose is certified by the manufacturer ((b) (4)

Potency Labeling

Each NUWIQ vial is labeled with the actual FVIII potency determined by one-stage clotting assay. Upon FDA's request, Octapharma added the word "Range" to the potency identifiers on the carton and container labels (such as "250 IU Range"). This format is consistent with labeling of other licensed FVIII products and is in accordance with the statements in Prescribing Information.

Stability of the Drug Product

The stability studies program included studies for long-term storage conditions and accelerated conditions and was found to be adequate. During the study, the samples were monitored for major specification parameters at pre-defined time periods. During review, a critical issue related to the (b) (4) parameter was identified and resolved, as described at the end of the CMC section. The available stability data supports the following shelf-life and in-use conditions.

- Bulk DS may be (b) (4) .
- Final DP may be stored for 24 months at 2 - 8°C when protected from light.
- During the shelf-life, the final DP may be kept at room temperature (up to 25°C) for a single period not exceeding three months; after this, the product must be used or discarded.
- The reconstituted DP solution must be used immediately or within three hours after reconstitution.

The manufacturer's plan for *Post-Marketing Stability Study* includes placing all four strengths of DP lots in storage, (b) (4) (at +5°C/ambient humidity, sealed, dark, upright) and regular monitoring for parameters indicative of stability. In conclusion, the stability study results support the proposed shelf-life of the DP, and the manufacturer's plan for post-marketing stability study is acceptable.

b) CBER Lot Release

Under the provision described in Federal Register (FR) 58:38771-38773 and the 60 FR 63048-63049 publication (8 December 1995), routine lot-by-lot release by CBER is not required for NUWIQ because it is a well-characterized recombinant product. Thus, exemption of NUWIQ from CBER Lot Release is justified.

CBER In-Support Testing

The Division of Biological Standards and Quality Control (DBSQC) performed in-support testing of commercial scale NUWIQ lots of 250 IU, and 2000 IU nominal potency. The results confirmed the suitability of critical quality-defining methods for their intended use as lot release specification tests. Test results were deemed consistent with the proposed commercial release specification.

c) Facilities Review / Inspection

Facility information in the BLA was reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of NUWIQ are listed in the table below. The activities performed and the inspectional history of the facilities involved in the manufacture of NUWIQ are listed in Table 2 and further described as follows.

Table 2. Manufacturing facilities for the Drug Product.

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Justification/ Results
(b) (4) *Drug Product Release Testing* Octapharma AB Elersvägen 40, SE 112 75 Stockholm, Sweden	3005559915	558833179	Pre-License Inspection	CBER 10/21/2014 – 10/28/2014 Voluntary Action Indicated (VAI)
Diluent - WFI (b) (4)	(b) (4)	(b) (4)	Waived	(b) (4) VAI
Primary labeling/packaging (b) (4)	(b) (4)	(b) (4)	Waived	(b) (4) VAI

CBER conducted a pre-license inspection of the Octapharma AB Stockholm facility (b) (4), DP and release testing) in October 21-24 and 27-28, 2014. Form 483 with 13 observations was issued. Deficiencies were noted in process validation, equipment validation, and management of the deviations. The company responded to the observations and the corrective actions were found to be adequate. All inspectional issues were considered satisfactorily resolved.

Team Biologics performed a surveillance inspection of the Octapharma (b) (4) manufacturing facility from (b) (4) All Form 483 issues were resolved and the inspection was classified as voluntary action indicated (VAI).

Team Biologics performed a surveillance inspection of th (b) (4) All Form 483 issues were resolved and the inspection was classified as VAI.

d) Environmental Assessment

The BLA included a request for a categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request was justified as the manufacture of this product does not alter significantly the concentration and distribution of naturally occurring substances, and no extraordinary circumstances exist that would require an environmental assessment.

SIGNIFICANT ISSUES RESOLVED DURING REVIEW OF THE BLA

1) Preliminary DP stability reports included multiple out-of-specification (OOS) results for the (b) (4) parameter analyzed by (b) (4) method. These OOS were not confirmed by subsequent studies, which indicated that they were caused by a deficiency in the testing procedure. Upon FDA request, Octapharma identified the root-causes for the OOS results as poor robustness of the (b) (4) method and (b) (4). In particular, during an FDA inspection of the facility in Stockholm (October, 2014), the Agency advised Octapharma to (b) (4) To help Octapharma develop the (b) (4) method, FDA indicated that it was willing to share its recent advances in this method.

Subsequently, Octapharma improved their (b) (4) method and re-evaluated the stability data. The re-evaluated data were found to be within the specifications at the subsequent stability time-points. Octapharma revalidated their improved (b) (4) method and re-analyzed retains of the clinical and validation lots of NUWIQ. All results are within the proposed specification for the (b) (4) assay by (b) (4). At the same time, Octapharma also committed to implement and validate a new (b) (4) method provided by FDA, re-analyze retains of the clinical and validation lots of NUWIQ using the (b) (4) method; and re-evaluate the specifications for (b) (4) (as described under Section 11.d) after BLA is approved.

2) Upon review of the stability study data, incorrect use of data were found related to European specifications that are based on nominal potency in the final DP vials. Octapharma re-evaluated these data using the U.S. market specification of (b) (4) of the labeled potency and found no substantial adverse potency trends during the product shelf-life.

3) Inspectional issues from the pre-license inspection as noted in the Facilities/Inspection section were satisfactorily resolved.

Chemistry, Manufacturing and Controls Conclusion

The manufacturing process for NUWIQ is considered validated to assure consistent manufacture of the product that meets acceptable release specifications. The reviewers from the Division of Hematology Research and Review in the Office of Blood Research and Review, the Division of Manufacturing and Product Quality, and the Division of Biological Standards and Quality Control in the Office of Compliance and Biologics Quality conclude that Octapharma has provided sufficient data and information on chemistry, manufacturing and controls to support the licensure of NUWIQ.

4. Nonclinical Pharmacology/Toxicology

Pharmacology Studies

These studies were conducted in a canine model of Hemophilia A and in normal, FVIII-replete (i.e. wild-type) rats. Hemophilic dogs that had been tolerized to human FVIII were dosed intravenously with increasing doses of NUWIQ, or an approved rFVIII product, or a pdFVIII concentrate in a cross-over study design. Dosing of hemophilic dogs with NUWIQ at doses approximately equivalent to the human starting dose restored the ex vivo whole blood clotting time (WBCT) activity and activated partial thromboplastin times (aPTT) to within normal limits, and the results were comparable to those obtained following dosing with the two approved FVIII

products. There were no effects of NUWIQ or the other FVIII preparations on the hematology profiles in the dogs as compared to prior to dosing (i.e., baseline), and no serious adverse effects or evidence of thrombogenicity were reported.

Secondary pharmacology studies with NUWIQ in FVIII-replete rats showed no elevations of ex vivo biomarkers of thrombosis at doses up to 14-fold greater than the maximum NUWIQ clinical dose. Biomarker results were similar to those achieved in rats dosed with the comparator rFVIII or pdFVIII products. No abnormal tissue pathology, and only sporadic evidence of in situ thrombosis with no apparent relationship in the incidence or severity to the FVIII dose level were observed on microscopic examination of lung and other tissues from rats dosed with NUWIQ.

In summary, the animal studies with NUWIQ showed the expected pharmacologic (pro-coagulant) activity in a canine model of Hemophilia A, and the results were similar to those obtained with other approved FVIII products. There was no evidence of undesirable secondary pharmacologic activity, i.e., thrombogenesis, in FVIII-replete rats dosed with NUWIQ at dose levels up to14-fold greater than the equivalent human NUWIQ starting dose. These data were used as proof-of-concept to support the rationale for entering NUWIQ into clinical trials, and to support the pharmacology section of the NUWIQ Package Insert (PI).

Pharmacokinetic Studies

These studies were conducted concurrently with the pharmacology studies in the Hemophilia A dogs, and FVIII activity was measured by both the one-stage clotting (OC) and chromogenic substrate (CS) assays. With both assays, the PK profiles from the dogs dosed with NUWIQ showed dose-dependent increases in all parameters measured, and were comparable to those obtained when the dogs were dosed with an approved rFVIII comparator product. Similar results were obtained in FVIII-replete, wild-type rats with NUWIQ and the two approved FVIII comparator products. A series of PK studies in FVIII-replete, wild-type rats and monkeys showed that the NUWIQ tested in the nonclinical safety program gave results that were comparable to the NUWIQ used in clinical trials, and that changes in manufacturing during the development program did not affect the critical PK parameters.

Toxicology Studies

Overall, toxicity studies with NUWIQ conducted in wild-type FVIII-replete rats, rabbits, and (b) (4) monkeys did not identify any unexpected findings or significant concerns. Monkeys dosed with a single intravenous injection of NUWIQ at doses up to 125-fold greater than the clinical starting dose demonstrated no systemic or tissue pathologies. A repeat dose toxicity study with NUWIQ was conducted in rats; animals were dosed daily for 28 days by bolus intravenous injection with NUWIQ doses equal to, and up to 14-fold greater than, the clinical starting dose. Although statistically significant differences in some measured parameters of toxicity were reported, the findings were not consistent or dose-related between the NUWIQ dose groups, and no corresponding histopathological findings were detected. The findings in rats following repeat dosing with NUWIQ were comparable to those findings in rats receiving equivalent doses of either an approved rFVIII or pdFVIII as comparators, suggesting that the safety profile of NUWIQ is similar to that of other approved FVIII products. In a 28-day, repeat dose toxicity study conducted in cynomolgus monkeys, animals were dosed daily by bolus intravenous injection with NUWIQ doses equal to, and up to 10-fold greater than, the clinical starting dose. Although statistically significant differences in some measured parameters of toxicity were reported, the findings were consistent and dose-related between the NUWIQ dose groups, and corresponding histopathological findings were detected. Animal findings for toxicity studies were expected and consistent, based on exaggerated pharmacologic effects for recombinant and plasma-derived FVIII products.

Dermal toxicity and local tolerance studies conducted in rabbits administered the clinical dose of NUWIQ revealed acceptable levels of inflammation and edema at the injection site.

There were no animal studies for carcinogenicity, in vivo mutagenicity, fertility, reproductive toxicity, or teratogenicity conducted with rFVIII. As rFVIII is a recombinant human protein, animals receiving repeated doses of the product developed antibodies against FVIII, which both accelerated its clearance and, in some individuals, neutralized its pro-coagulant activity. Therefore, long-term, repeat-dose toxicity studies as well as the standard carcinogenicity bioassay (i.e., 2 years of daily rFVIII dosing in both rats and mice) were not feasible to conduct.

Because rFVIII is a protein, the standard genotoxicity testing recommended in the ICH S2 guidance documents would not provide information to address potential mutagenicity of rFVIII and as per the ICH S6 guidance on biotechnology-derived protein therapeutics, these studies were not required. The lack of carcinogenicity, mutagenicity, and chronic toxicity data are addressed in the appropriate section of the package insert for NUWIQ.

No nonclinical reproductive or developmental toxicity studies were conducted. As Hemophilia A affects mostly male subjects, it is highly unlikely that a pregnant or lactating woman would receive NUWIQ. NUWIQ labeling includes a statement that nonclinical reproductive and developmental toxicity studies have not been conducted, and NUWIQ should be used only if clearly needed during pregnancy or lactation. This labeling is consistent with that included in prescribing information for other approved recombinant human coagulation factors for the treatment of Hemophilia A.

Nonclinical Pharmacology/Toxicology Conclusion

The results from the nonclinical program suggest that the safety profile of NUWIQ is sufficient to support its use for the proposed indications of on-demand treatment and control of bleeding episodes, perioperative management of bleeding, and routine prophylaxis to reduce the frequency of bleeding episodes in adults and children with Hemophilia A.

5. Clinical Pharmacology

The clinical pharmacokinetics of NUWIQ has been assessed in 5 clinical studies. GENA-01, GENA-03 and GENA-09 included a full analysis of PK parameters. In the remaining two supportive studies, GENA-04 (extension study of GENA-09) and GENA-08, only in vivo recovery (IVR) data were collected. PK studies for gender, race, and drug-drug interactions have not been conducted.

GENA-01 was a prospective, randomized, actively controlled, open-label, multicenter phase 2 study in previously treated patients (PTPs) with severe Hemophilia A (FVIII:C $\leq$1%). This study enrolled 22 PTPs between 12 and 65 years of age. After baseline PK assessments, they were randomized to receive either NUWIQ followed by Kogenate FS or Kogenate FS followed by NUWIQ in a crossover design to establish bioequivalence. In addition to the baseline PK assessment, a 3-month IVR assessment and a 6-month PK assessment were performed for NUWIQ only. Blood samples for the determination of FVIII plasma levels were taken before infusion and up to 48 hours after the end of the infusion. Patients received a dose of 50 IU/kg and blood samples were analyzed for FVIII levels using both the OC and the CS assays. Pharmacokinetic (PK) data analysis was performed using non-compartmental analysis. NUWIQ was found to be bioequivalent to Kogenate. OC assay-based PK parameters (Mean $\pm$ SD, N = 22) for NUWIQ at a dose of 50

IU/kg were: T1/2 = 17.1 ± 11.2 h, IVR = 2.14 ± 0.27 % - per IU/kg, and clearance (CL) = 2.96 ± 0.97 mL/hr/kg. Similar results were obtained with the CS assay. Overall, the PK profile of NUWIQ at 6 months was generally comparable to the profile measured at study start (first dose). After 3 months and after 6 months of treatment with NUWIQ, the mean IVR values were within the range of 2.0 to 2.5% per IU/kg.

GENA-03 was a prospective, non-controlled, open label, multinational, multicenter phase 3 study in children diagnosed with severe Hemophilia A (FVIII:C <1%) with at least 50 previous exposure days (EDs) to FVIII concentrates. Twenty-six patients underwent PK analysis with their previous FVIII concentrate and NUWIQ. Of these, 13 patients were between 2 and 5 years of age, and 13 were between 6 and 12 years of age. Blood samples for the determination of FVIII plasma levels were taken before infusion, 30 minutes, and 2, 5, 10, 24, and 48 hours after the end of the infusion. IVR assessments were performed at baseline, and after 3 and 6 months of treatment in all patients. Pediatric patients received a dose of 50 IU/kg and blood samples were analyzed for FVIII levels using both the OC and CS assays. PK data analysis was performed using non-compartmental analysis. For children aged 2 to 5 years the OC assay based PK parameters (Mean ± SD) for NUWIQ were: T1/2 = 11.9 ± 5.4 h, IVR = 1.6 ± 0.2 % per IU/kg, and CL = 5.4 ± 2.3 mL/hr/kg. For children aged 6 to 12 years the OC assay based PK parameters (Mean ± SD) for NUWIQ were: T1/2 = 13.1 ± 2.6 h, IVR = 1.6 ± 0.4 % per IU/kg, and CL = 4.1 ± 0.9 mL/hr/kg. Mean incremental IVRs according to the CS assay ranged from 1.568–1.834% per IU/kg. Compared to adults, there appears to be a substantial increase in mean body weight adjusted systemic CL (+83%) in pediatric patients 2 to < 6 years of age. The difference between adult CL and pediatric CL for the age range 6-12 years was less pronounced (+37%). These differences should be taken into account when dosing children 2 to 12 years of age. Similar results were obtained with data from the CS assay.

GENA-09 was a prospective, open-label, single-center, phase 2 study in PTPs with severe Hemophilia A (FVIII:C ≤1%) with a randomized crossover PK part and an uncontrolled prophylaxis part. This study enrolled 22 PTPs between 18 and 62 years of age. PTPs received a dose of 50 IU/kg of Kogenate or NUWIQ. Blood samples were analyzed for FVIII levels using both OC and CS assays. PK data analysis was performed using non-compartmental analysis. NUWIQ was found to be bioequivalent to Kogenate. OC assay-based PK parameters (Mean ± SD, N = 22) for NUWIQ at a dose of 50 IU/kg were: T1/2 = 11.43 ± 3.94 h, IVR = 2.19 ± 0.555 % per IU/kg, and CL = 3.94 ± 1.44 mL/hr/kg. Similar results were obtained with the CS assay. Mean incremental IVR at baseline, after 3 months, and after 6 months for NUWIQ was comparable between time points as determined with the OC assay (2.2, 2.1 and 2.3 % per IU/kg, respectively). Overall, PK parameters for NUWIQ at 6 months were consistent with those obtained at study start (first dose).

GENA-04 and GENA-08 were prospective, open-label, phase 3 studies in PTPs with severe Hemophilia A (FVIII:C ≤1%). Only IVR was calculated at study entry and after several months of treatment. Patients received a dose of 50 IU/kg of NUWIQ and blood samples were analyzed for FVIII levels using both OC and CS assays. Both studies showed that for the OC assay, the mean IVR over time was in the range of 1.52 to 2.20 % per IU/kg, while for the CS assay the mean IVR over time was in the range of 1.77 to 2.57 % per IU/kg. After multiple dosing, the results of IVR did not change.

Clinical Pharmacology Conclusion

No critical issues were found during the data review. In general, all presented study designs, results, and conclusions were found to be acceptable.

6. Clinical/Statistical

a) Clinical Program

Summary of Clinical Trials

Clinical trials for NUWIQ were conducted under IND 13722. Data from three clinical trials and two additional (non-IND) trials were submitted to support the safety and efficacy of NUWIQ for the proposed indications. There was no formal hypothesis testing of efficacy in these trials. All trials enrolled subjects who were previously treated with a FVIII product (≥150 exposure days [ED] in subjects ≥12 years of age, and ≥50 ED in subjects <12 years of age). Two additional non-IND trials (GENA-09 and GENA-04, an extension of GENA-09) were carried out at a single foreign center in subjects with chronically undertreated disease and more severe clinical sequelae. These trials are summarized in Table 3.

Table 3. Clinical Trials.

Trial ID (Type)	Trial Design	Objectives	Subjects (N=135)	Regimen	Treatment Duration
GENA-01 (PK, Efficacy, Safety, Immunogenicity) IND	Open-label, multicenter, phase 2, PK, on-demand treatment, and perioperative management arms	1) To compare PK of NUWIQ with active comparator 2) To investigate immunogenic potential 3) To assess clinical efficacy and safety in treating BE 4) To assess efficacy and safety in perioperative management	PTPs 12 to 65 years of age; 2 adolescents (one age 12, one age 17) **22** enrolled[1]; 21 completed[2] 22 in PK group 21 in on-demand group 2 in perioperative group	PK: Single dose 50 IU/kg On-demand treatment of BE: Initial dose 20 to 60 IU/kg Perioperative management: Initial dose 25 to 50 IU/kg	≥50 ED and ≥6 months
GENA-08 (PK, Efficacy, Safety, Immunogenicity) IND	Prospective, open-label, multicenter, phase 3, PK and prophylaxis arms.	1) To test the efficacy of NUWIQ during prophylaxis, in the treatment of BE and in perioperative management 2) To investigate the immunogenic potential of NUWIQ 3) To assess the safety of NUWIQ	PTPs 18 to 75 years of age; **32** enrolled; 26 completed 6 protocol exclusions 26 in prophylaxis group 5 in perioperative group.	PK: Single dose 50 IU/kg Routine prophylaxis: Beginning dose 30-40 IU/kg every other day Perioperative management: Initial dose 20 to 50 IU/kg	PK: 6 months Routine prophylaxis: ≥50 ED and ≥6 months
GENA-03 (Efficacy,	Prospective, open-label,	In children: 1) To compare	PTPs 2 to 11 years of age; one	PK: Single	≥ 50 ED and ≥6 months

Immunogenicity, PK, Safety) IND	multicenter, phase 3, PK	PK of NUWIQ with active comparator 2) To investigate immunogenic potential 3) To assess clinical efficacy and safety in treating BE 4) To assess efficacy and safety in surgical prophylaxis	12 years of age **59** enrolled 26 in PK group[3]; 13 subjects 2 to 5 years of age, 13 subjects 6 to 12 years of age. 56 in prophylaxis group 5 in perioperative group (and 1 withdrawn for Von Willebrand disease)	dose 50 IU/kg <u>Routine prophylaxis</u>: Beginning dose 30-40 IU/kg every other day or three times per week <u>Perioperative management</u>: Initial dose 20 to 50 IU/kg	
GENA-09 (PK, Efficacy, Safety) Non-IND	Single center (Russia), prospective, randomized, cross-over, open-label, phase 2	1) To compare PK of NUWIQ with active comparator 2) To test the efficacy of NUWIQ during prophylaxis, in the treatment of breakthrough BE, and in perioperative management 3) To investigate the immunogenic potential of NUWIQ 4) To assess the safety of NUWIQ	PTPs 18 to 62 years of age; **22** enrolled; 22 in PK group 21 in prophylaxis group 4 in perioperative group	<u>PK</u>: Single dose 50 IU/kg <u>Routine prophylaxis</u>: Beginning dose 30 IU/kg every other day <u>Perioperative management</u>: Initial dose 25 to 50 IU/kg	≥ 50 ED and ≥6 months
GENA-04 (Non-IN D, Extension of GENA-09) (No new subjects enrolled)	Single center (Russia), open-label extension of GENA-09	1) To assess long-term immunogenicity and tolerability of NUWIQ 2) To assess clinical efficacy in treating breakthrough BE 3) To assess efficacy in routine	PTPs 18 to 62 years of age who participated in GENA-09; 18 enrolled; 1 withdrew consent, 1 protocol violation, 16 completed. 16 in PK group 16 in prophylaxis	<u>PK:</u> Single dose 50 IU/kg <u>Routine prophylaxis</u>: Beginning dose 30 IU/kg every other day	Until local supply of NUWIQ depleted

		prophylaxis	group 3 in perioperative group	Perioperative management: Initial dose 25 to 50 IU/kg	

Abbreviations: ED=Exposure days; IU/kg = international units per kilogram; PK = pharmacokinetic; PTP = previously treated patients. BE = bleeding episode(s)

[1] Enrolled = received at least one dose of product

[2] Completed = completed per protocol

[3] Full PK measurements. All subjects had in vivo recovery (IVR)

Overall, 135 subjects completed clinical trials of NUWIQ and there were 1208 bleeding episodes (BE) across the five trials. In general, dosing was in line with dosing for other FVIII products. Of the 135 subjects, all had severe Hemophilia A (FVIII < 1%), all were male, and all had a significant prior exposure to FVIII products (>150 ED in adults and > 50 ED in children). Of the subjects in the IND trials, the majority (91.4%) was White; African Americans and Asians accounted for 3.7% each.

b) Efficacy Analysis

On-Demand Treatment

Response to treatment was assessed using the following scale:

- *Excellent*: Abrupt pain relief and/or unequivocal improvement in objective signs of bleeding within approximately 8 hours after a single infusion;
- *Good*: Definite pain relief and/or improvement in signs of bleeding within approximately 8 to 12 hours after an infusion, requiring up to 2 infusions for complete resolution;
- *Moderate*: Probable or slight beneficial effect within approximately 12 hours after the first infusion, requiring more than two infusions for complete resolution;
- *None*: No improvement within 12 hours, or worsening of symptoms, requiring more than 2 infusions for complete resolution.

In the three IND trials for on demand treatment there were 1124 BE. Overall efficacy in these three trials was excellent in 60-71%, good in 11-34%, moderate in 5.5-15% and none in 1.9%. Efficacy was generally higher for minor BE than it was for moderate to major BE. The median number of doses required was 1.0 (range 1 to 22). The median doses in GENA-01 and GENA-08 were 30.0 and 33.3 IU/kg, respectively, across all severities of BE in these two adult trials, and 43.9 IU/kg in the pediatric trial GENA-03. In the largest trial (GENA-01), 91.4% of BE required treatment with a single infusion and 5.8% required two infusions. In the two other trials, (GENA-08 and GENA-03), 68% and 81.5% required a single infusion, and 12.7% and 7.4% required two infusions, respectively.

As for other FVIII preparations, the recommended dosing of NUWIQ for on-demand treatment varies with the severity of the bleeding and on the measured level of FVIII. The treatment schedule was similar to that of other FVIII products. Subjects in the Russian study GENA-09 required 50% more infusions, possibly explained by the poor baseline condition of these subjects. Children generally received a slightly higher dose (IU per kg), and this was potentially attributable to the known PK differences in children, and that at the time of these trials only the 500 IU vials were available. In general whole vials were administered, so doses tended to be rounded up to avoid underdosing.

Routine Prophylaxis

Two of the IND trials (GENA-03 and GENA-08) evaluated routine prophylaxis. The criteria for study success were (1) the reduction in the annualized bleeding rate (ABR) compared to the on-

demand subjects in GENA-01, and (2) the frequency of spontaneous breakthrough BE after ≥50 ED at the end of the trial, using the following rating scale (normalized to ABR):

- *Excellent*: <0.75 spontaneous BE per month;
- *Good*: Between 0.75 and 1 spontaneous BE per month;
- *Moderate*: Between1 and 1.5 spontaneous BE per month;
- *Poor*: >1.5 spontaneous BE per month.

ABR of prophylaxis versus on-demand treatment
The mean ABR of 58.08 (95% CI 44.43 to 71.73) with on-demand treatment in GENA-01 was decreased with prophylactic treatment to 2.28 in GENA-08 (95% CI 0.94 to 3.63), and to 4.12 (95% CI 2.76 to 5.48) in GENA-03. These 96% (GENA-08) and 93% (GENA-03) reductions in ABR for prophylactic treatment compared to on-demand treatment (GENA-01) exceeded the a priori efficacy criterion of a >50% reduction in ABR.

Treatment of spontaneous breakthrough BE
GENA-08: Treatment results were excellent for the 26 spontaneous BE that occurred. For all 44 BE, which includes those due to trauma, results were excellent or good in 97% of events.
GENA-03: Treatment results were excellent in 94.9%, good in 1.7% and moderate in 3.4% of the 36 spontaneous breakthroughs BE. For all 108 BE (includes traumatic BE) results were excellent in 77 (71.2%), good in 12(11.1%), moderate in 17 (15.7%) and poor in 2 (1.9%). Efficacy was similar in the two pediatric age groups.

Supportive trials
In a non-IND trial of long term prophylaxis (GENA-04) the overall efficacy was deemed excellent in 94% and good in 6% of subjects, with an improvement in joint health and bleeding rates compared to baseline values prior to prophylactic treatment. The overall prophylactic efficacy in the study GENA-09 was rated as excellent or good in 91% of subjects. The incidence of BEs in these two later studies was higher than in the other trials and was generally more severe. However, the outcomes in these two supportive trials, where subjects generally were inadequately treated prior to the trial and had longstanding sequelae, suggest that even in patients with poor prior control of their bleeding disorder, long term prophylaxis can improve outcome.

<u>Perioperative Management</u>
Use of NUWIQ in a total of 19 subjects undergoing 34 perioperative treatments across the five trials support the indication for perioperative surgical prophylaxis. Of these procedures, 20 were minor and 14 were major. Major operations were classified prospectively as:

- Requiring general or spinal anesthesia;
- Requiring opening into the great body cavities;
- Requiring hemostasis for ≥6 days;
- Joint surgery;
- Extraction of the third molar or ≥3 teeth;
- Conditions in which the patient's life is at stake.

Efficacy was assessed using the following rating scales:
Intraoperative

- *Excellent*: Blood loss ≤ the average expected blood loss in a similar patient with normal hemostasis;
- *Good*: Blood loss higher than the average expected blood loss in a similar patient with normal hemostasis;

- *Moderate*: Blood loss higher than the maximal expected blood loss in a similar patient with normal hemostasis, but hemostasis was controlled;
- *None*: Hemostasis was uncontrolled necessitating a change in clotting factor replacement regimen;

Postoperative

- *Excellent*: No postoperative bleeding or oozing that was not due to complications of surgery. All postoperative bleeding (due to complications of surgery) was controlled with NUWIQ as anticipated for the type of procedure;
- *Good*: No postoperative bleeding or oozing that was not due to complications of surgery. Control of postoperative bleeding due to complications of surgery required increased dosing with NUWIQ or additional infusions, not originally anticipated for the type of procedure;
- *Moderate*: Some postoperative bleeding and oozing that was not due to complications of surgery; control of postoperative bleeding required increased dosing with *NUWIQ* or additional infusions, not originally anticipated for the type of procedure;
- *None*: Extensive uncontrolled postoperative bleeding and oozing. Control of postoperative bleeding required use of an alternate FVIII concentrate.

Efficacy was rated as excellent or good in 100% of minor surgery cases and 92% of major operations (one was rated as moderate) as described in Table 4.

Table 4. Perioperative Efficacy.

Study	**Number of Operations**	**Efficacy Ratings**
GENA-01	2 major 1 minor	No NUWIQ used
GENA-08	4 major	3- excellent 1- good intraoperative and moderate postoperative
	1 minor	All Excellent
GENA-03	6 major 1- excluded[1]	All Excellent
GENA-09	14 minor	All Excellent
GENA-04	3 major	All Good
	4 minor	All Excellent

[1] Diagnosed as Von Willebrand disease and withdrawn from study

c) Pediatric Study and PREA Requirements

NUWIQ is not exempt from PREA requirements. The pediatric trial (GENA-03) demonstrated adequate safety and efficacy for the use of NUWIQ in 59 children 2 to 12 years of age. In addition there were two adolescents ages 12 and 17 included in GENA-01. Safe and effective use in children <2 years of age can be extrapolated. No post-marketing pediatric studies are required for this product.

d) Other Special Populations
As Hemophilia A occurs almost exclusively in males, no females were included in any of the trials. The trials did not include any subjects over 65 years of age.

e) **Bioresearch Monitoring**
Bioresearch Monitoring (BIMO) inspections were conducted for three foreign clinical investigator study sites, and did not reveal any issues that impact the data in this submission.

7. Safety

The following safety endpoints were used to assess NUWIQ:

- Immunogenicity – Development of inhibitors (as identified by Nijmegen modification of the Bethesda assay) and non-inhibitory anti-rFVIII antibodies;
- Vital signs;
- Laboratory assessments (hematology, clinical chemistry);
- General tolerability and AE monitoring. AE were assessed as mild, moderate or severe, serious or non-serious, and expected or unexpected using definitions predefined in the protocols. AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 15.1.

Data from the completed pivotal trials (GENA-01,-03, and -08), as well as the two supportive trials (GENA-09 and -04) trials were analyzed to allow for an integrated review of safety topics. There was a total of 272 AEs in 79 subjects. The most common System Organ Class was infections and infestations (57 subjects). Most AEs were in children and reflected common childhood illnesses.

There were 11 Serious Adverse Events (SAEs) in eight subjects in the three IND trials. These are summarized in Table 5.

Table 5. SAEs.

System Organ Class Preferred Term	No. of Subjects (%)
Gastrointestinal Disorders	
Hepatic cirrhosis	1 (0.7)
Hepatic encephalopathy	1 (0.7)
Infections and Infestations	
Device-related infection	1 (0.7)
Tonsillitis	1 (0.7)
Upper respiratory infection	1 (0.7)
Lower respiratory infection	1 (0.7)
Injury, Poisoning, and Procedural Complications	
Head injury	2 (1.4)
Traumatic fracture	1 (0.7)
Musculoskeletal and Connective Tissue Disorder	
Hemarthrosis	1 (0.7)
Psychiatric Disorders	
Depression, suicidal	1 (0.7)

All subjects recovered from the SAEs with the exception of subject 010202 (in GENA 01) with hepatic cirrhosis. All SAEs were assessed by both the investigator and the FDA reviewer as unrelated to NUWIQ. In reviewing the safety data, no new safety signals were identified during the clinical trials for NUWIQ.

Immunogenicity

No cases of FVIII inhibitor formation were recorded in any of the subjects in all trials with NUWIQ. Low titer, non-inhibitory antibodies were detected in four subjects. All were present at screening; two were transient and were absent by three to six months despite continued treatment with NUWIQ.

AEs of special interest

There were no severe allergic reactions or thrombotic events observed in any subject in any trial.

Overall Clinical Assessment/Conclusions

NUWIQ demonstrated adequate efficacy with an acceptable safety profile in pediatric and adult patients with Hemophilia A, and the clinical reviewer recommends approval.

8. Advisory Committee Meeting

The Division of Hematology Research and Review and the Division of Hematology Clinical Review in the Office of Blood Research and Review reviewed the information in BLA STN 125555/0 for NUWIQ / Antihemophilic Factor (Recombinant), rAHF and determined that referral to the Blood Products Advisory Committee (BPAC) prior to approval was not needed because of the following.

- The product's mechanism of action is well understood.
- Review of the data did not reveal safety or efficacy concerns, or pose unanswered scientific questions that would benefit from advisory committee discussion and recommendation [FDAAA (HR 3580-138 SEC. 918: Referral to Advisory Committee)].

9. Other Relevant Regulatory Issues

There were no other regulatory issues raised during the review of STN BLA 125555/0.

10. Labeling

The proposed proprietary name for the product, NUWIQ, was reviewed by the Advertising and Promotional Labeling Branch (APLB) and recommended to be acceptable on September 2, 2014. The product labeling (i.e., prescribing information, patient package insert, and instructions for use) and the product package and container labels were reviewed, commented, and/or revised by the appropriate discipline reviewers before APLB conducted its review from a promotional and comprehension perspective.

FDA comments and recommendations regarding the product labeling and labels were initially conveyed to Octapharma on April 29, 2015, and negotiated throughout the months of May to September 2015.

NUWIQ was found acceptable as the proprietary name for the product by the agency on September 4, 2014. Final versions of the product labeling and labels submitted to the BLA on September 2, 2015 were considered acceptable.

11. Recommendations and Risk/Benefit Assessment

a) Recommended Regulatory Action

The CBER review committee recommends approval of this BLA. The manufacturing process for NUWIQ was found validated and adequately controlled. Efficacy and safety clinical data for NUWIQ supported a favorable benefit/risk determination for the proposed indications.

- On demand treatment and control of bleeding episodes.
- Perioperative management of bleeding.
- Routine prophylaxis to reduce the frequency of bleeding episodes.

b) Benefit/Risk Assessment

Hemophilia A patients are at risk for acute bleeding episodes predominantly into joints, muscles, mucosa, and body cavities. Repeated bleeding into a joint can lead to disabling joint disease. NUWIQ replaces the missing FVIII that is needed to achieve hemostasis in patients with Hemophilia A. In recent years, treatment regimens have shifted from on-demand treatment of bleeding episodes to routine prophylaxis due to observed improvement in long-term clinical outcomes such as joint damage. NUWIQ is a human recombinant FVIII produced in a human cell line with human post-translational modification. The cell line utilizes cultivation media entirely devoid of animal- or human-derived materials.

Benefits

The efficacy of NUWIQ has been established for on-demand treatment and control, perioperative management and routine prophylaxis, using data from three pivotal and two supportive (non-IND) trials. 135 adult and pediatric subjects complied with the trial protocol. They experienced 1124 bleeding episodes and 19 of the subjects underwent 34 surgical procedures.

Risks

The formation of FVIII inhibitors (neutralizing antibodies) was not observed during the three pivotal and two supportive trials. Even though no subjects developed FVIII inhibitors, the potential for their developing is included in the Warnings and Precautions section of the Package Insert. Low titer, non-inhibitory antibodies were detected in four subjects. All were present at screening; two were transient and were absent by three to six months despite continued treatment with NUWIQ. No serious adverse events were found to be attributable to NUWIQ.

Overall Benefit/Risk Profile

The overall benefit/risk profile of NUWIQ is favorable. Clinical studies demonstrated efficacy of NUWIQ for its labeled indications. No serious adverse events were attributable to the drug.

c) Recommendation for Post Marketing Risk Management Activities

There was no safety issue identified that warrants a Risk Evaluation and Mitigation Strategy (REMS) or post-marketing requirement (PMR). A routine pharmacovigilance plan is recommended and no new post-marketing risk mitigation management activities are requested. The review committee agreed with the post-marketing surveillance plans and post-marketing studies proposed by Octapharma in their Pharmacovigilance Plan (listed below under PMCs II.1-5). These

planned studies may provide additional efficacy and safety information related to the use of NUWIQ in specific treatment subpopulations.

d) Post Marketing Commitments

I. To resolve the remaining CMC issue with validation of the (b) (4) assay used for the (b) (4) parameter of the DP specification, which was considered to not be critical for the BLA approval (refer to Section 3, above), Octapharma committed to the following activities.

1. Octapharma commits to validate and implement the (b) (4) received from FDA, for (b) (4) analysis as a quality control lot release test for NUWIQ and submit for approval by FDA as a Prior Approval Supplement (PAS) by 04 September 2016 under a Supplement that contains Post Marketing Study Commitment – Final Study Report.

II. The following studies are planned by Octapharma (with projected start and end dates) and should be considered clinical PMCs:

1. GENA-05: Evaluation of immunogenicity, efficacy and safety of Antihemophilic Factor (Recombinant) in previously untreated patients.
Final protocol submission date: November 2, 2012
Study/trial completion date: November 30, 2018.
Final Report Submission date: April 30, 2019.

2. GENA-13: Evaluation of long-term immunogenicity, tolerability, and efficacy of Antihemophilic Factor (Recombinant) in previously treated children.
Final protocol submission date: September 17, 2015
Study/trial completion date: June 30, 2016.
Final Report Submission date: November 30, 2016.

3. GENA-15: Extension for subjects who completed GENA-05.
Final protocol submission date: December 12, 2013
Study/trial completion date: November 30, 2018.
Final Report Submission date: April 30, 2019.

4. GENA-99: Post-licensure trial to document long-term immunogenicity, safety, and efficacy of Antihemophilic Factor (Recombinant) in patients treated in normal clinical.
Final protocol submission date: July 21, 2014
Study/trial completion date: June 30, 2019.
Final Report Submission date: March 31, 2020.

5. European Haemophilia Safety Surveillance Study: Will evaluate inhibitor development, hypersensitivity reactions, thromboembolic events, and medication errors in a home setting.

12. References

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