Application Type	Original Application
STN	125555/0
CBER Received Date	June 5, 2014
PDUFA Goal Date	June 5, 2015
Division / Office	DHRR /OBRR
Priority Review	No
Reviewer Name(s)	Victor C. Baum
Review Completion Date / Stamped Date	
Supervisory Concurrence	
Applicant	Octapharma Pharmazeutika Produktionsges.m.b.H.
Established Name	Antihemophilic Factor (Recombinant) Plasma/albumin free
(Proposed) Trade Name	NUWIQ®
Pharmacologic Class	B-domain-deleted recombinant coagulation factor VIII expressed in genetically modified human embryonic kidney cells
Formulation(s), including Adjuvants, etc	Intravenous injection
Dosage Form(s) and Route(s) of Administration	Lyophylized powder in single-dose vials containing 250, 500, 1000 or 2000 international units to be reconstituted with 2.5 mL sterile water in a pre-filled single-dose syringe, Intravenous
Dosing Regimen	Required IU = body weight (kg) x desired Factor VIII rise % (IU per dL) x 0.5 (IU per kg per IU per dL) OR Expected Factor VIII rise (% normal) = 2 x administered IU/body weight (kg) Dosing for long term prophylaxis: 30-40 IU per kg every other day. Every

	other day or three times per week in children.
Indication(s) and Intended Population(s)	Control and prevention of bleeding episodes and for perioperative management in adults and children with Hemophilia A.
Orphan Designated (Yes/No)	No

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GLOSSARY

AE	adverse event(s)
AUC	area under the curve
AUC norm	AUC normalized for dose
BE	bleeding episode(s)
BHK	baby hamster kidney
BMI	body mass index (kg/m2)
CHO	Chinese hamster ovary
CHR	chromogenic assay
CL	clearance
Cmax	maximum plasma concentration
ED	exposure days
FVIII	factor VIII
FVIII:C	FVIII activity
HEK	human embryonic kidney
Human-cl rhFVIII	human cell line recombinant human FVIII [NUWIQ®]
ITT	intention to treat
IU	international unit
IVR	in vivo recovery
MRT	mean residence time
OS	one stage assay
pd	plasma-derived
PK	pharmacokinetic
PTM	post-translational modification
rFVIII	recombinant factor VIII
rhFVIII	human cell line recombinant human FVIII [NUWIQ®]
SAE	serious adverse event
t1/2	half-life
Tmax	time at maximum concentration

1. EXECUTIVE SUMMARY

STN 125555 is an original biologics license application (BLA) submitted by Octapharma for a recombinant factor VIII (rFVIII) under the trade name NUWIQ®. It is a fourth generation B-domain-deleted rFVIII expressed in human embryonic kidney (HEK-293) cells. The B-domain is dispensable for coagulation activity. The proposed indication for Nuwiq® is control and prevention of bleeding episodes (and for perioperative management) in adults and children with Hemophilia A. Since the product is prepared in a human cell line and no animal proteins are used in the manufacturing process, it is also indicated in hemophilia patients with known allergic reactions to either mouse or hamster proteins. It also avoids potential transmission of known or unknown blood borne pathogens.

This product is the second recombinant FVIII concentrate to be produced in a human cell line with human post-translational modification machinery and to employ cultivation media entirely devoid of animal- or human-derived materials. The rationale for using a human cell line for rFVIII expression is to more closely mimic the pattern of post-translational modification of endogenous FVIII, resulting in elimination of potentially antigenic epitopes created during production in non-human cells. Glycosylation was shown to be similar to native FVIII. Human-specific post-translational modification may

have a particular benefit in reducing the development of FVIII inhibitors. In vitro studies showed that this modified FVIII had comparable coagulation and vonWillebrand-binding activity as full-length rFVIII products containing the B domain.

Three pivotal clinical trials are submitted in support of this application as well as two additional supportive (non-IND) studies that support the safety and efficacy of this product and the proposed indication in children and adults: "Control and prevention of bleeding episodes and for perioperative management in adults and children with Hemophilia A". These pivotal trials are GENA-01 (22 subjects), a pharmacokinetic trial with secondary safety and efficacy outcomes in adults, GENA-08 (32 subjects), an efficacy trial with secondary PK outcomes in adults, and GENA-03 (59 subjects), an efficacy trial in children 2-5 and 6-12 years of age (which supports the indication for use in children). All studies reported here 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 (GENA-09 and a follow up trial GENA-04) were carried out at a single Russian center in subjects with chronically undertreated disease and more severe clinical sequelae.

Overall NUWIQ® was evaluated in 135 subjects across the five trials and 1208 bleeding episodes. In general, dosing was in line with that for other FVIII products, and was similar in children and adults. Of the 135 subjects all had severe hemophilia A (FVIII < 1%), all were male and all had significant prior exposure to FVIII. 59 subjects were children (2-12 years of age).

The overall prophylactic efficiency (given every other day in adults and every other day or three times a week in children) was rated as excellent or good in 100% of subjects (GENA-08) and 97% (GENA-03). Results were 91% and 100% excellent or good in the two supporting studies. Monthly bleeding rates across the trials ranged from 0.095-0.24 bleeding episodes per month and met FDA's *a priori* definition of efficacy. The outcomes in the two supportive trials, where subjects generally were inadequately treated prior to the trial and had longstanding sequelae, suggest that even in relatively poorly controlled patients long term prophylaxis can improve outcome. However, the incidence of bleeding episodes in these two later studies was higher than in the other trials and was generally more severe. The rate of traumatic (versus spontaneous) bleeding episodes observed in children was higher than in adults, which is expected given the higher activity levels in children.

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 is similar to that of other FVIII products. The median number of infusions was 1 (range 1-22) with a mean dose of 32-45 IU per kg in the three IND studies. Subjects in the non-IND Russian trial 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), although this was potentially explainable in that at the time only the 500 IU vials were available, and in general whole vials were administered so doses tended to be rounded to avoid underdosing. Unaddressed were the minor pharmacokinetic differences between children and adults that might also partially account for this finding.

Use in a total of 34 surgical cases in 20 subjects across the five trials support an indication for perioperative surgical prophylaxis. Of these procedures 20 were minor and 14 were major. Efficacy was rated as excellent or good in 100% of minor cases and 92% of major operations (one was rated as moderate).

In a non-IND trial of long term prophylaxis (GENA-04) the overall efficacy was deemed excellent in 94% and good in 6%, and efficacy in treating bleeding episodes in this trial was good or excellent in 84% of bleeding episodes, with an improvement in joint health and bleeding rates compared to baseline values prior to prophylactic treatment.

In 59 pediatric patients (2-12 years of age) with severe hemophilia prophylactic treatment was rated as excellent or good in 97% of subjects and efficacy in treating bleeding episodes was rated as excellent or good in 82% of episodes, despite the 62% incidence of traumatic bleeding in this pediatric population. There was no difference in treatment response between the 2-5 and 6-12 year old age groups. Perioperative efficacy was also demonstrated in these pediatric groups, although the number of operations was small (N=6) and most were of limited extent.

There were no safety signals. All serious adverse events (SAEs) were assessed as unrelated to the product.

Inhibitor formation (anti-FVIII antibodies) can occur in up to 30% of patients treated with FVIII. Other rFVIII preparations have resulted in inhibitor formation in 8-42% of previously untreated pediatric patients. The incidences have been higher in second generation products than with third generation products. No cases of FVIII inhibitor formation were recorded in any of the subjects in these trials with NUWIQ®. Non-inhibitory antibodies were detected in four subjects. These were all low titer.

Overall this product demonstrated excellent efficacy with an excellent safety profile. It potentially offers less inhibitor formation than some other currently available products due to the human post-translational modifications of the protein. Although the BLA indicates that this is “the first rFVIII concentrate to be produced in a human cell line with human post-translational modification (PTM) machinery and to employ cultivation media entirely devoid of animal- or human-derived materials”, a recently approved product, Eloctate™ (Biogen) is also prepared from human embryonic kidney cells into a culture medium without animal proteins or human sources.

The pediatric trial (GENA-03) demonstrated adequate efficacy and safety in a pediatric population to support use in children. Safe and effective use in children <2 years of age can be extrapolated. No post-marketing studies are required for this product. The applicant has proposed four post-marketing studies sponsored by Octapharma and participation in a broader European hemophilia trial.

Recommendation:
Based on my review of the submitted, data NUWIQ® appears safe and effective in pediatric and adult patients with hemophilia A. An approval is recommended. Approval for an indication of prophylaxis is also recommended, however it is noted that this is not specifically requested on the draft label.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Hemophilia A (hemophilia) is an X-linked coagulopathy in which affected individuals (almost entirely males) do not produce adequate functional FVIII to achieve satisfactory hemostasis. It is the most common of the severe inherited coagulopathies with an incidence of approximately 1 in 10,000 births, with approximately 20,000 males in the United States affected. Disease severity is classified by the level of FVIII activity (FVIII:C): mild (5 to <40% of normal), moderate (1-5%) and severe (<1%). The most common sequelae are recurrent bleeding episodes (BE), particularly in joints and muscles. These can occur shortly after birth with circumcision or with immunizations. Repeated hemarthroses and hematomas can produce long term disabilities. Additional sites for BE include the central nervous system, the genitourinary and gastrointestinal tracts, the eyes and the retroperitoneum. Bleeding from surgical trauma, even minor procedures such as tooth extraction, can be life-threatening.

Fifty years ago the average life expectancy was less than 20 years with quality of life severely limited by joint complications and intracranial hemorrhage. Prognosis has been markedly improved with the introduction of replacement therapies (Refer to Section 2.3). Replacement therapy is typically begun in children at the time of the first joint bleed and primary prophylaxis with a rFVIII product is currently the preferred treatment for children with severe disease. Prophylaxis has been shown to prevent complications later in life and to decrease the incidence of inhibitor formation (Refer to Section 2.3). Delayed prophylaxis is referred to as secondary prophylaxis. Even secondary prophylaxis can reduce the frequency of BE. The typical prophylactic regimen is 25-40 IU per kg every other day for three times per week, although an intermediate dose of 15-25 IU per kg is sometimes used.

The most serious complication of treatment in hemophilia is inhibitor formation, which occurs in up to 30% of patients with severe hemophilia A.[1]

The first generation licensed rFVIII products were produced in hamster cells and included Recombinate (Bayer; also claimed by Wyeth as Recombinate, which was developed by Genetic Institutes, which today is part of Wyeth; approved in 1992) and Helixate FS (Bayer; approved in 1993). These products used media enriched with human or animal plasma proteins for initial cell culture and contained albumin in the final formulation. For second generation products, such as Helixate FS/Kogenate FS® (Bayer/CSLBehring) and ReFacto® (Wyeth), sucrose was substituted for albumin in the final formulation. Third generation products, such as Advate® (Baxter) and Xyntha® / ReFacto AF® (Pfizer) do not contain any human or animal plasma proteins in the purification or final formulation.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Additional therapeutic options include:

1 Gouw SC, van der Bom JG, Ljung R, *et al*. Factor VIII products and inhibitor development in severe hemophilia A. *N Engl J Med*. 2013;368:231-9.

- Antifibrinolytic therapy to delay clot dissolution can be used as a secondary, nonspecific, adjunctive therapy but this is not a primary treatment option. These medications such as epsilon-aminocaproic acid and tranexamic acid help preserve the hemostatic plug. They are typically used for mucocutaneous bleeding from the mouth or nose and for dental procedures.
- Desmopressin (DDAVP) is an arginine vasopressin analogue that causes a transient rise in FVIII and vonWillebrand factor. It is typically used for mild hemophilia.

2.3 Safety and Efficacy of Pharmacologically Related Products

Pathogen transmission and inhibitor formation are the main safety concerns when treating hemophilia patients with FVIII replacement therapy. The availability of recombinant FVIII products reduces the risk of pathogen transmission, but not inhibitor development.

Clinical management and life expectancy were markedly improved by the introduction of cryoprecipitate, and subsequently plasma-derived (pd) FVIII concentrates to provide replacement FVIII. Unfortunately many patients were infected by HIV during the 1980s from plasma-derived products. Concerns about transmission of blood-borne pathogens have been ameliorated by the development of recombinant products. Full-length and modified rFVIII have been produced in Chinese hamster ovary (CHO) or baby hamster kidney (BHK) cells. Several such products have been approved. An additional newly approved rFVIII product, Eloctate™ is also produced from human embryonic kidney (HEK) cells as is NUWIQ®.

Potential problems with these products, even the rFVIII products include the development of neutralizing antibodies (inhibitors) and the potential for allergic reactions to animal-based proteins remaining from the synthetic process. The development of inhibitors decreases the efficacy of replacement therapy, increases the risk of unmanageable bleeding and increases cost of treatment (by 3-5 fold)2. The incidence of inhibitor development is approximately 30% in severe disease and less in mild or moderate disease. The highest incidence is in previously untreated patients with severe disease (reported from 3-52%). Inhibitor development in previously treated patients is less, reported as 0.9-4%. Potential risk factors for inhibitor development include genetic factors such as the type of FVIII gene mutation, human leucocyte antigen (HLA) type, polymorphisms in immune regulatory regions, family history of inhibitors and ethnic background as well as immunologic environment during early treatment and high intensity of treatment (either peak acute treatment or high overall treatment frequency). The reported incidences of inhibitor formation in comparator products has been reported as 0-2.3% (Kogenate), 0.5-0.9% (Advate), 2.9% (Recombinate), 0.9-2.2% for ReFacto/Xyntha BDD, and 0% (Eloctate).

The current product was developed from human cells with the intention of providing a new rFVIII from a human cell line that is potentially less immunogenic. No animal

2 Goudemand J: hemophilia. Treatment of patients with inhibitors: cost issues. *Haemophilia* 2013;5:397-491.

Gringeri A, Mantovani LG, Scalone L, Mannucci PM: Cost of care and quality of life for patients with hemophilia complicated by inhibitors: the COCIS Study Group. *Blood* 2003; 102:2358-2363.

proteins are used in the purification process and no human albumin is used as a stabilizer, in distinction to other similar rFVIII products. The rationale for using a human cell line for rFVIII expression was to more closely mimic the pattern of PTMs of endogenous FVIII, resulting in elimination of potentially antigenic epitopes created during production in non-human cells. Human-specific PTMs may have a particular benefit in reducing the development of FVIII inhibitors. For example, N-glycolylneuraminic acid (Neu5Gc), which is reported to be antigenic in humans and is present in recombinant glycoproteins expressed by CHO cells, is not detected in rhFVIII. Furthermore, the antigenic carbohydrate epitope Gal-α1-3βGalβ1-(3)4GlcNAc-R (α-Gal), which has been reported to be present in recombinant proteins such as full-length FVIII from baby hamster kidney (BHK) cells, is not present in rhFVIII.

Although the BLA alleges that this will be the first rFVIII produced in a human cell line with human post-translational modification (PTM) machinery and to employ cultivation media entirely devoid of animal- or human-derived materials, a recently approved product, Eloctate®, also meets these criteria. Eloctate®, which is a B-domain deleted rhFVIII covalently linked to the human IgG_1 FC domain, has a prolonged half-life (19.7 hours after a single dose, versus 14.7 hours for NUWIQ®), with levels >1% for five days (prophylactic dosing interval every 3-5 days, more frequently in children <6 years old).

2.4 Previous Human Experience with the Product (Including Foreign Experience)

NUWIQ® is currently approved in the European Union, Australia and Canada. Between July 22, 2014 (the International Birth Date) and November 30, 2014 (the date of the Periodic Safety Update Report) approximately 458,250 IU were sold. Four clinical trials currently with 171 subjects are ongoing. There have been no regulatory actions related to safety or marketing experience. There have been no individual case safety reports received from commercially available drug.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

During a type B (end of phase 2) meeting on Nov. 7, 2012 (CRMTS#8660) FDA proposed that prophylactic efficacy would be established with at least a 50% decrement in the annualized bleeding rate in a prophylaxis versus an on-demand treatment arm. This was accomplished by comparing the BE rates in GENA-08 with the on-demand only treatment in GENA-01. Prophylactic efficacy was confirmed in these analyses. A further request by FDA (pre-BLA meeting Sept. 12, 2013, CRMTS#9039) requested a modified statistical analysis. In this meeting FDA agreed that the PK, efficacy, safety and immunogenicity data from GENA-01, GENA-08 and GENA-03 would suffice for submission of a BLA to support an indication of “control and prevention of bleeding episodes in adults and children with Hemophilia A”. FDA required that NUWIQ® have a true inhibitor rate <6.8%, and this has also been demonstrated in these studies (0% overall development of inhibitors).

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty. It was submitted

electronically and formatted as an electronic Common Technical Document (eCTD) according to FDA guidance for electronic submission. This submission consisted of the five modules in the common technical document structure.

3.2 Compliance With Good Clinical Practices And Submission Integrity

The studies supporting this submission were conducted in compliance with good clinical practices, including informed consent, site-specific issues, and in accordance with acceptable ethical standards.

Three clinical investigators were inspected by CBER Bioresearch Monitoring (BIMO) in support of the BLA and were conducted in accordance with FDA's Compliance Program Guidance Manual (CPGM) 7348.811, Inspection Program for Clinical Investigators.

Site Number	Study Site	Location	Enrolled Subjects	FDA Form 483 issued	Classification
03-41 GENA-03	University Medical School	Warsaw, Poland	17	Yes	VAI
03-43 GENA-03	Medical University of Silesia	Zabrze, Poland	6	Yes	VAI
08-14 GENA-08	Royal Hallamshire Hospital	Sheffield, UK	5	No	NAI

VAI = Voluntary Action Indicated; NAI = No Action Indicated

Sponsor-identified protocol deviations

- Trial GENA-01: 22 subjects had ≥1 minor protocol deviation. Several were due to not respecting the 72 hour washout limit. Four subjects received another FVIII product during the on-demand phase.
- Trial GENA-08: 31 subjects had ≥1 minor protocol deviation. Five subjects had major deviations (>5 days between two consecutive prophylactic doses).
- Trial GENA-03: 57 subjects had ≥1 minor violation. Major violations occurred in three subjects. One was belatedly diagnosed as vonWillebrand disease and two others received a dose outside the targeted dose range. (As described this may have been due to dose rounding to the next whole vial).

The outlined protocol violation/deviations did not undermine the quality of the trial data and the overall trial conclusions were not invalidated.

3.3 Financial Disclosures

Covered clinical study (name and/or number): GENA-01		
Was a list of clinical investigators provided:	Yes X☐	No ☐ (Request list from applicant)
Total number of investigators identified: 9		
Number of investigators who are sponsor employees (including both full-time and part-		

time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Covered clinical study (name and/or number): GENA-11		
Was a list of clinical investigators provided:	Yes X☐	No ☐ (Request list from applicant)
Total number of investigators identified: 5		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		

Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Covered clinical study (name and/or number): GENA-08		
Was a list of clinical investigators provided:	Yes X☐	No ☐ (Request list from applicant)
Total number of investigators identified: 11		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Covered clinical study (name and/or number): GENA-03		
Was a list of clinical investigators provided:	Yes X☐	No ☐ (Request list from

		applicant)
Total number of investigators identified: 15		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

NUWIK® consists of a single molecule of B-domain deleted human coagulation FVIII. The drug substance is produced in a human embryonic kidney 293 (HEK-293) cell line. NUWIK® is a white sterile lyophilized powder and solvent for solution for injection. The lyophilized powder is supplied in single-dose vials containing 250 IU, 500 IU, 1000 IU, and 2000 IU of recombinant factor VIII per vial. Before use, the lyophilized powder is reconstituted with a single-dose solvent pre-filled syringe containing 2.5 mL of sterilized water for injections. The reconstituted solution is a clear, colorless solution, practically free from visible particles, containing 100 IU / 200 IU / 400 IU /800 IU FVIII:C/ per mL. The concentration of each of the excipients is the same for all strengths, only the recombinant FVIII concentration varies. Excipients are: sucrose, sodium chloride, calcium chloride, arginine hydrochloride, sodium citrate, and Poloxamer 188.

Selected Specifications for NUWIQ®

Test Parameter	**Analytic Procedure**	**Acceptance Criteria**

Appearance	Visual inspection	Clear, colorless solution practically free from visible particles
(b) (4)	(b) (4)	(b) (4)
Identity	(b) (4) (b) (4)	Complies
Specific FVIII:C activity	Calculated from potency and content	(b) (4)

4.2 Assay Validation

All key laboratory parameters were measured in the same certified USA-based central laboratory by the same validated methods. FVIII concentration in subjects' plasma was measured by both the one-stage and chromogenic assays; both were shown to accurately measure rFVIII (NUWIQ) FVIII inhibitors were assessed by the Nijmegen modification of Bethesda assay with two different test bases: normal human plasma and congenital FVIII-depleted human plasma spiked with rhFVIII. The time points for testing of inhibitory and non-inhibitory antibodies were the same in all studies.

4.3 Nonclinical Pharmacology/Toxicology

An in vitro study (b) (4) with *in silico* follow up analysis of overlapping peptide spanning sequences (replacing the B-domain) showed no evidence of T cell epitopes compared to 59 healthy donors. A second somewhat similar study showed that positive T cell responses were decreased with the addition of von Willebrand factor. An additional in vitro study showed a low risk of clinical immunogenicity.

In dogs, recoveries of NUWIQ® and the comparator ReFacto (a recombinant B-domain-deleted FVIII) were similar, with similar half-lives, but only two animals were studied, limiting generalizability. A study in dogs with hemophilia-A compared NUWIQ® with ReFacto and showed equivalent efficacy (i,e. cuticle bleeding, partial thromboplastin time, plasma FVIII levels, and whole blood clotting times). There was no inhibitor formation with NUWIQ®.

In toxicologic studies, a study of 10 rats receiving a dose of 10,000 IU per kg resulted in no deaths or clinical signs of toxicity. The highest non-lethal intravenous dose of the product was >10,000 IU per kg. A repeated-dose toxicity study in (b) (4) monkeys gave animals daily injections for one week followed by injections at weeks 1 , 2 and 3. An additional group continued to receive 1500 IU per kg on alternate days from day 29-day 41. There were no deaths or treatment-related clinical effects. PK parameters were appropriate. Animals receiving higher doses developed low levels of inhibitors as expected with a human-derived protein. A second study in (b) (4) monkeys compared NUWIQ® to Amofil, a pd-FVIII. Animals received NUWIQ® 50 or 500 IU per kg per day or vehicle control for four weeks, with some assigned also to a two week follow up. Other animals received the comparator. Results were similar with both agents, however the initial increase in FVIII activity and the subsequent fall in activity from anti-FVIII antibodies was greater in the animals receiving NUWIQ®.

A perivenous injection study in rabbits showed no macroscopic or microscopic evidence of dermal irritation.

4.4 Clinical Pharmacology

Evaluation of the clinical pharmacology of NUWIQ® in subjects with hemophilia was part of all three IND clinical trials and one non-IND trial.

4.4.1 Mechanism of Action

NUWIQ® contains the active substance human recombinant coagulation FVIII. As such it temporarily restores the inadequate levels of FVIII found in hemophilia A and allows for adequate hemostasis. Upon activation of the clotting cascade, FVIII is converted to activated FVIII and acts as a cofactor for activated factor IX, accelerating the conversion of factor X to activated factor X on phospholipid surfaces, which ultimately converts prothrombin to thrombin and leads to the formation of a fibrin clot.

4.4.2 Human Pharmacodynamics (PD)

The pharmacodynamic effects of recombinant human FVIII are the same as those of the endogenous coagulation FVIII. NUWIQ® has binding to vonWillebrand factor similar to that of native FVIII

4.4.3 Human Pharmacokinetics (PK)

Table 1

PK parameter	**Chromogenic assay Mean ± SD**	**One-stage clotting assay Mean ± SD**
AUC (h·IU/mL)	22.6 ± 7.8	18.0 ± 5.6
AUC_{norm} (h·IU/mL/(IU/kg))	0.4 ± 0.1	0.4 ± 0.1
$C_{maxnorm}$ (IU/mL/(IU/kg))	0.025 ± 0.004	0.022 ± 0.003
$T_{1/2}$ (h)	14.7 ± 10.0*	17.1 ± 11.2#
IVR (%/IU/kg)	2.5 ± 0.4	2.1 ± 0.3
MRT (h)	19.5 ± 12.0	22.5 ± 14.2
CL (mL/h/kg)	2.9 ± 1.2	3.0 ± 1.0
V_{ss} (mL/kg)	49.6 ± 17.3	59.8 ± 19.8

Source: Package insert

The PK characteristics of NUWIQ® were similar to those of the full length comparator Kogenate FS (GENA-01), and the bioequivalence of NUWIQ® and Kogenate (requested by FDA) were shown to be similar in this study. The $T_{1/2}$ of NUWIQ® was slightly higher than that reported for other rFVIII products (except Octate®). PK parameters with prolonged administration (>6 months of treatment) were evaluated in GENA-01 and GENA-09 and no significant changes were seen with prolonged, repeated exposure. This was confirmed in GENA-01, -08, -09 and -04 where recovery was measured at 3-monthly intervals up to as long as 21 months without changes over time.

4.5 Statistical

All studies met their predefined efficacy endpoints and there were no statistical issues of concern.

4.6 Pharmacovigilance

Octapharma maintains a Corporate Drug Safety Unit that collects and collates information about suspected adverse reactions and prepares appropriate safety and ADR reports.

The following studies are planned (with projected start and end dates):

1. GENA-05: Immunogenicity, Efficacy and Safety of Treatment with Human-cl rhFVIII in Previously Untreated Patients with Severe Haemophilia A

    - Final protocol submission date: November 2, 2012
    - Study/trial completion date: November 30, 2018
    - Final Report Submission date: April 30, 2019

2. GENA-13: Clinical Study in Previously Treated Children with severe Haemophilia A to Investigate the Long-Term Immunogenicity, Tolerability and Efficacy of Human-cl rhFVIII

    - 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 Study for Patients who completed GENA-05 (NuProtect) – to Investigate Immunogenicity, Efficacy and Safety of Treatment with Human-cl rhFVIII

    - Final protocol submission date: December 12, 2013
    - Study/trial completion date: November 30, 2018
    - Final Report Submission date: April 30, 2019

4. GENA-99: Prospective, multinational, non-interventional post-authorisation study to document the long-term immunogenicity, safety, and efficacy of Human-cl rhFVIII in patients with haemophilia A treated in routine clinical practice

    - 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

Reviewer Comment: The incidence of inhibitor formation in GENA-15 will be important. The incidence of inhibitor formation is highest in previously untreated patients, and all subjects in the current studies had a significant prior exposure history, by design.

Areas for postmarketing pharmacovigilence

- Immunogenicity profile and safety in previously untreated subjects (to be addressed in Trial GENA-05 and others)

- Tolerance in the general population (to be addressed in Trial GENA-13 and others)
- Thromboembolic phenomena [review individual case study reports (ICSRs) from post-marketing
- safety surveillance; European Haemophilia Safety Surveillance Study (EUHASS)]
- Maladministration/handling errors in home use (MedDRA queries, Post-marketing study and EUHASS)
- Safety in children < 2 years old (review ICSRs from post-marketing, Trial GENA-05)
- Safety in elderly patients (review ICSRs from post-marketing safety surveillance)
- Safety in pregnant and breast feeding women (review ICSRs from post-marketing safety surveillance)
- Safety in patients with renal or hepatic impairment (review ICSRs from post-marketing safety surveillance)
- Safety in patients with mild or moderate hemophilia A (review ICSRs from post-marketing safety surveillance)
- Safety in patients with high risk gene mutations(review ICSRs from post-marketing safety surveillance)
- Safety in patients with different ethnic origins (review ICSRs from post-marketing safety surveillance)
- Safety in patients with HIV or other infections (review ICSRs from post-marketing safety surveillance)
- Safety and efficacy of immune tolerance induction (review ICSRs from post-marketing safety surveillance)

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

Five clinical studies are presented. Two, GENA-09 and its extension GENA-04 were non-IND studies undertaken in a group or chronically undertreated subjects at a single Russian institution. They are not pivotal studies and are not discussed in detail in section 6. These two studies evaluated a type of patient not now commonly encountered in medically developed countries. GENA-09 used a randomized crossover design to compare PK parameters with Kogenate/Kogenate FS, a licensed full length rFVIII product. This review, then, focuses on the three IND studies, all of which are pivotal.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

1.2 Cover Letter
1.3.3 Debarment Certification
1.3.4 Financial Disclosure
1.3.5.1 Patent Information
1.12.1 Pre IND Correspondence
1.12.4 Request for Comments and Advice on an IND
1.14.1 Draft Labeling
1.16 Risk Management Plans
2.2 Introduction
2.4 Nonclinical Overview

2.5 Clinical Overview
4 Nonclinical Study Reports
5 Clinical Study Reports

5.3 Table of Studies/Clinical Trials

Table 2

Protocol	Type	# Subjects	Primary Endpoint
GENA-01*	Prospective, randomized, crossover, open-label, multicenter, multinational, phase 2	22 (12-65 yr)	PK vs. Comparator
GENA-08*	Prospective, open-label, , multicenter, multinational, phase 3	32 (18-75 yr)	Efficacy, Prophylaxis, treatment, surgical prophylaxis
GENA-03*	Prospective, non-controlled, open-label, pediatric, multicenter, multinational, phase 3	59 (1-2 and 6-12 yr)	Efficacy, Pediatric prevention and treatment
GENA-09†	Prospective, randomized, cross-over, open-label, single center, phase 2	22 (18-62 yr)	PK vs. Comparator
GENA-04†	Open-label extension of GENA-09, single center, phase 2	18 (18-62 yr)	Safety, long term; Extension of GENA-09

*** Primary analysis; † Supportive**

5.4.1 Advisory Committee Meeting (if applicable)

5.4.2 External Consults/Collaborations

5.5 Literature Reviewed (if applicable)

1. Gouw SC, van der Bom JG, Ljung R, *et al*. Factor VIII products and inhibitor development in severe hemophilia A. *N Engl J Med*. 2013 Jan 17;368(3):231-9.
2. Goudemand J: hemophilia. Treatment of patients with inhibitors: cost issues. Haemophilia 2013;5:397-491.
3. Gringeri A, Mantovani LG, Scalone L, Mannucci PM: Cost of care and quality of life for patients with hemophilia complicated by inhibitors: the COCIS Study Group. Blood 2003; 102:2358-2363.

6. Discussion of Individual Studies/Clinical Trials

All studies reported here enrolled subjects who were previously treated (≥150 exposure days in subjects ≥12 years of age and ≥50 exposure days in subjects <12 years of age).

6.1 Trial #1

GENA-01: Clinical Study To Investigate The Pharmacokinetics, Efficacy, Safety And Immunogenicity Of Human-cl rhFVIII, A Newly Developed Human Cell-Line Derived Recombinant FVIII Concentrate In Previously Treated Patients With Severe Haemophilia A

6.1.1 Objectives (Primary, Secondary, etc)

Primary Objective: Compare PK (FVIII:C) of NUWIK® to Kogenate FS, a licensed FVIII product in patients with severe hemophilia previously treated with FVIII.

Secondary Objectives:

- To calculate the incremental recovery of FVIII:C for *Human-cl rhFVIII (NUWIQ®)*
- To investigate the immunogenic potential of *Human-cl rhFVIII*
- To assess clinical efficacy and safety of *Human-cl rhFVIII* in the treatment of bleeding episodes (BE)
- To assess clinical efficacy and safety of *Human-cl rhFVIII* in surgical prophylaxis

6.1.2 Design Overview

A prospective, randomized, open-label, crossover, multicenter phase 2 trial in previously treated patients with severe hemophilia. In part I the PK of NUWIQ® was compared to Kogenate FS (50 IU FVIII) in a 1:1 ratio. Following a washout period of ≥96 hours subjects received 50 IU per kg of the alternate. Subjects completing part I were followed for ≥6 months [≥50 exposure days (ED)] during which on-demand treatments with NUWIQ® were documented. Data were also accumulated if subjects required surgical procedures.

6.1.3 Population

22 male subjects (of 20-25 planned)

Inclusion Criteria
Male 12 to 65 years of age with severe hemophilia (FVIII:C<1%)
25-110 kg
Previous FVIII treatment (≥150 ED)
Immunocompetent ($CD4^+$>200/µL)
HIV negative

Exclusion Criteria
Coagulation disorder other than hemophilia A
Present or past FVIII inhibitor (≥0.6 Bethesda units)
Severe liver or kidney disease (AST>5 times upper limit of normal, creatinine >120 µM/L)

Overall, 22, males age range 12-65 years of age with severe hemophilia (FVIII:C ≤1%) and normal body habitus were enrolled. Subjects had to have had ≥150 ED of FVIII concentrate and be immune competent.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Part I: Subjects received 50 IU per kg study drug in random order
Part II: On demand treatment of spontaneous or traumatic BE:
Minor hemorrhage (superficial muscle or soft tissue and oral bleeds): 20-30 IU per kg every 12-24 hours until BE resolution
Moderate-major hemorrhage (hemorrhage into muscles, into oral cavity; haemarthrosis; known trauma): 30-40 IU per kg every 12-24 hours until

BE resolution

Major-life threatening (intracranial, intra-abdominal, gastro-intestinal or intrathoracic bleeds, central nervous system bleeds, bleeding in retropharyngeal spaces or iliopsoas sheath, eyes/retina, fractures or head trauma): 50-60 IU per kg initially then 20-25 IU per kg every 8-12 hours until BE resolution

Surgical prophylaxis:

Minor (e.g. tooth extraction): 25-30 IU per kg ≤ 3 hours preoperatively, intended to reach level of 50-60% (of normal). Repeated every 12-24 hours to maintain trough level of approximately 30%.

Major: 50 IU per kg ≤3 hours preoperatively intended to reach level of 100%. Repeat if necessary after 6-12 hours for at least six days to maintain trough level or approximately 50%.

6.1.6 Sites and Centers

USA (6 sites), Germany (2 sites), Bulgaria (1 site)

6.1.7 Surveillance/Monitoring

Efficacy and safety data (including inhibitor data) were monitored by an Independent Data Monitoring Committee composed of recognized experts in the field of hemophilia clinical care who were not actively recruiting subjects.

6.1.8 Endpoints and Criteria for Study Success

Primary objective: To determine the pharmacokinetics (PK) NUWIQ® (FVIII:C) and to compare it with the licensed FVIII concentrate Kogenate FS.

Secondary Objectives:

• To calculate the incremental recovery of FVIII:C for *NUWIQ*®
• To investigate the immunogenic potential of *NUWIQ*®
• To assess clinical efficacy and safety of *NUWIQ*® in the treatment of bleeding episodes
• To assess clinical efficacy and safety of NUWIQ® in surgical prophylaxis

PK parameters included:

- AUC
- T1/2
- Maximum plasma concentration (C_{max})
- Time at maximum concentration (T_{max})
- Mean residence time (MRT)
- Clearance (CL)

Efficacy Measures

In vivo recovery

On-demand treatment:

Subjective assessment by subject:

- 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 8–12 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

Surgical prophylaxis

Efficacy assessed at end of surgery by surgeon and postoperatively by surgeon and hematologist. In addition, pre- intra- and postoperative FVIII plasma levels

Safety Measures

- Development of inhibitor activity at trial entry, immediately before both treatment cycles, in the 48 hour PK sample, after 10-15 ED with NUWIQ® and at three months, then every three months. Preoperatively if surgery required.
- Hematologic, clinical chemistry and urinalyses at multiple time points
- Incidence of Adverse Events (AE)

6.1.9 Statistical Considerations & Statistical Analysis Plan

The 90% confidence of the ratio or log-ratio of NUWIQ®:Kogenate FS for PK parameters and a separate analysis to test whether the ratio of mean AUCs was within 0.8-1.25.

The null hypothesis H_0 for successful treatment (excellent or good) at the end of BE was P≤0.7. On demand treatment was deemed successful if the lower confidence limit was >0.7. In a secondary analysis the severity of bleeding was included. A secondary hypothesis was tested, namely the proportion of BE resolved with 1-2 infusions of NUWIQ®.

For immunogenicity analysis, data from this trial were to be pooled with those from other clinical studies such that N>100.

6.1.10 Study Population and Disposition

All 22 subjects were included in the safety and intention-to-treat populations.

6.1.10.1 Populations Enrolled/Analyzed

- 14 subjects who completed the trial are included in the per-protocol population.
- 22 subjects receiving both treatments in part I are included in the per-protocol PK population
- 21 subjects completed the PK analysis after 6 months (6m-PP population)
- 22 subjects had 986 BE treated with NUWIQ® (BLEED population); 669 BE in the 14 subjects in the per-protocol population
- 2 subjects required surgery during which NUWIQ® was used

6.1.10.1.1 Demographics

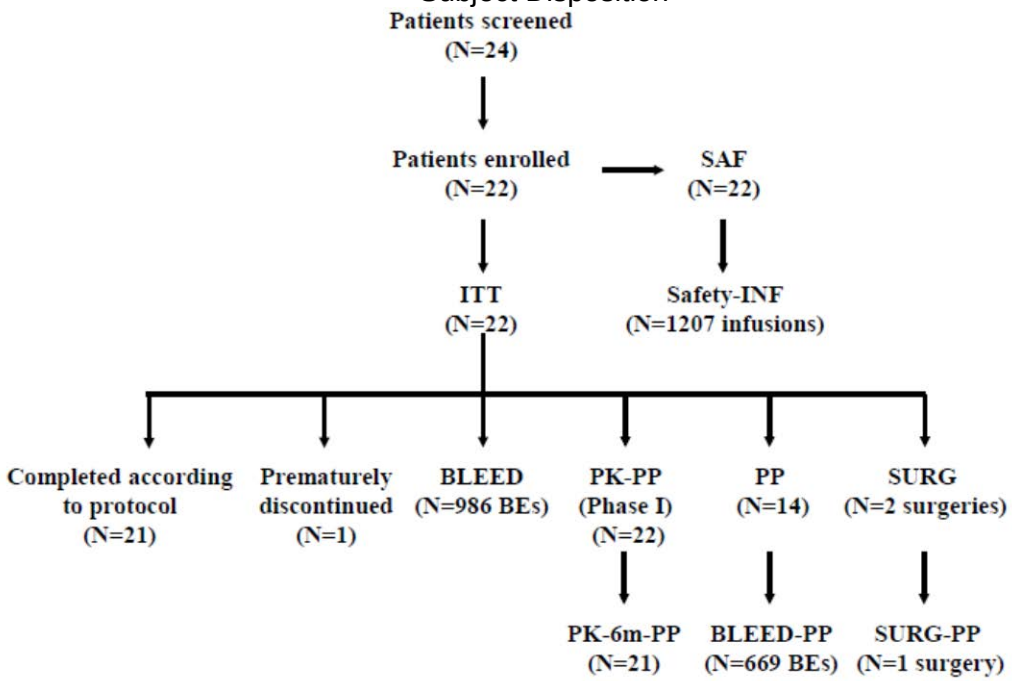
Of the 22 subjects 18 were white (2 Hispanic or Latino), three were African American and one was American Indian. All were male. The mean weight was 72.7 kg. BMI ranged from 18.7 to 35.0 with a mean of 24 kg per m^2. Six subjects were from Bulgaria, six from Germany and 10 from the United States. Fourteen had a family history of hemophilia and two had a family history of inhibitors.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
All subjects had severe hemophilia (FVIII:C <1%) and had at least 150 ED to FVIII concentrate. All were immunocompetent ($CD4^+$ count >200 per µL)

6.1.10.1.3 Subject Disposition

Disposition of subjects from Trial GENA-01 is illustrated in Figure 1 below, reproduced from the application

Figure 1
Subject Disposition



BE = bleeding episode; BLEED = study population of BEs treated with NUWIQ®; ITT = intention-to-treat; PK = study population of patients undergoing pharmacokinetic analysis; PK-6m = study population of patients undergoing pharmacokinetic analysis at 6 months; PP = per-protocol; SAF = study population of patients in safety analysis; Safety-INF = study population of NUIQ infusions; SURG = study population of surgeries treated with NUWIQ®.
Source: original BLA 12555/0; Section 5.3.3.2Clinical Study Report p 56.

No subject discontinued participation due to an adverse event (AE). One terminated early due to loss of follow up at 291 days (after the 6-month visit). Prior to that he had received 27 administrations.

6.1.11 Efficacy Analyses

Efficacy results are based on the intention to treat (ITT) dataset.

6.1.11.1 Analyses of Primary Endpoint(s)

Table 3
PK at Study Entry

PK parameter	NUWIQ®	Kogenate FS	Result
AUC (norm) - CHR [h x IU/mL/(IU/kg)]	0.39	0.38	Similar
AUC (norm) - OS	0.37	0.38	Similar
IVR - CHR (%/IU/kg)	2.5	2.49	Similar
IVR - OS	2.14 ±0.27	2.03 ± 0.28	Similar
CL – CHR (mL/kg/h)	2.94 ± 1.18	2.75 ± 0.64	Similar
CL - OS	2.96 ± 0.97	2.82 ± 0.72	Similar
T 1/2 - CHR (h)	14.73 ± 9.96	16.14 ± 5.88	NUWIQ® slightly shorter
T 1/2 - OS	17.05 ± 11.23	18.75 ± 5.94	NUWIQ® slightly shorter

Table 4
PK at 6 Months

PK parameter	NUWIQ®	Result
AUC (norm) - CHR [h x IU/mL/(IU/kg)]	0.36	Similar to entry data
AUC (norm) - OS	0.34	Similar to entry data
IVR - CHR (%/IU/kg)	2.37	Similar to entry data
IVR - OS	2.05	Similar to entry data
CL - CHR (mL/kg/h)	3.33	Similar to entry data
CL - OS	3.39	Higher than at study entry
T 1/2 - CHR (h)	12.65 ± 4.07	Lower than at study entry
T 1/2 - OS	14.05	Slightly shorter (due to single outlier)

Reviewer Comment: Because some atypical data were obtained from some Bulgarian subjects, data were analyzed excluding subjects from Bulgaria. In this instance there were no differences between PK values at entry and at 6 months

Table 5

6 Month Data Excluding Bulgarian Subjects

PK parameter		Result
AUC (norm) - CHR [h x IU/mL/(IU/kg)]	0.35	Similar to entry data
AUC (norm) - OS		
IVR - CHR (%/IU/kg)	2.07	Similar to entry data
IVR - OS		

CL - OS(mL/kg/h)	3.13	Similar to entry data
CL - OS		
T 1/2 - CHR (h)	14.57	Similar to entry data

6.1.11.2 Analyses of Secondary Endpoints

- Immunogenic potential: No subjects developed inhibitors
- Clinical efficacy in the treatment of BEs: 986 BEs were treated with NUWIQ® (15-93 per patient): 65% spontaneous, 35% traumatic and 0.3% other. 42% were minor, 57% moderate to major in severity and 0.3% life-threatening. The use of NUWIQ and the efficacy are summarized in Tables 6 and 7 below. Clinical efficacy in surgical prophylaxis: There were only two surgical procedures, one major and one minor. Efficacy rating was excellent for both.

  Reviewer Comment: No subjects were FVIII product naïve. The incidence of inhibitors is much lower in previously treated patients.

Table 6
Treatment of Bleeding Episodes (N=986)

Parameter	Mean	SD	Median	Range
Number of infusions per bleeding site*	1.1	0.59	1.0	1-13
Dose of *Human-cl rhFVIII* per infusion, IU	2375	1055	2000	500-6000
Dose of *Human-cl rhFVIII* per infusion, IU/kg	32.3	10.59	30.0	7-61
Number of EDs per BE*	1.1	0.55	1.0	1-13
Dose of *Human-cl rhFVIII* per BE, IU	2693	2618	2000	500-65,000
Dose of *Human-cl rhFVIII* per BE, IU/kg	36.6	27.64	30.9	8-657

* Dosage used to treat several simultaneous bleedings are counted only once in this analysis.
BE = bleeding episode; BLEED = study population of BEs treated with *Human-cl rhFVIII*; ED = exposure day; IU = international unit; SD = standard deviation.
Source: Section 14, Tables 14.2.28, 14.2.29 and 14.2.31.

Source: original BLA 12555/0; Section 5.3.3.2Clinical Study Report p 75.

Table 7
Efficacy

Severity of BE (number of BEs) Efficacy rating	N	%
Any	986	100
Excellent	595	60.3
Good	336	34.1
Moderate	54	5.5
None	-	-
Missing	1	0.1
Minor	416	100.0
Excellent	312	75.0
Good	98	23.6
Moderate	6	1.4
None	-	-
Missing	-	-
Moderate to major	566	100.0
Excellent	283	50.0
Good	236	41.7
Moderate	47	8.3
None	-	-
Missing	-	-
Major to life-threatening	3	100.0
Excellent	-	-
Good	2	66.7
Moderate	1	33.3
None	-	-
Missing	-	-
Unknown	1	100
Excellent	-	-
Good	-	-
Moderate	-	-
None	-	-
Missing	1	100

BE = bleeding episode; BLEED = study population of BEs treated with *Human-cl rhFVIII*.
Source: Section 14, Table 14.2.25.1.

Source: original BLA 12555/0; Section 5.3.3.2Clinical Study Report p 77.

Reviewer Comment: These data meet the primary endpoint and establish adequate efficacy for treatment of BE. However the number of surgical procedures in this trial (N=2) was inadequate for these data alone to support an indication for surgical prophylaxis.

6.1.11.3 Subpopulation Analyses

There were inadequate data in this adult male trial to analyze by race or investigational site.

6.1.11.4 Dropouts and/or Discontinuations

Two subjects were excluded for protocol violations (at days 180 and 52, after 88 and 26 drug administrations) and one for therapy failure at day 71 (44 administrations).

6.1.12 Safety Analyses

6.1.12.1 Methods

All subjects comprised the safety set, based on the ITT dataset. All but one were included in the 6 month per protocol population. The frequencies of all AEs was by system organ class and preferred term, coded according to the Medical Dictionary for Regulatory Activities V15.1.

6.1.12.2 Overview of Adverse Events

Three serious adverse events (SAEs) developed in two subjects (suicidal depression in one subject and worsening hepatic cirrhosis and hepatic encephalopathy in another); two of these were severe. In total there were seven total SAEs in three subjects: suicidal depression in one subject, hepatic cirrhosis, abdominal pain, peripheral neuropathy and peripheral edema in one subject, and constipation in the third subject. Overall, 12 patients (54.5%) developed a total of 69 treatment-emergent AE (herein after referred to as AE) after 41/1207 infusions. The most common AE were gastrointestinal disorders (12 subjects), pyrexia (2) and proteinuria (2). There were no patterns with regard to AE occurrence and the phase of the trial, or with age of the subject.

6.1.12.3 Deaths

There were no deaths.

6.1.12.4 Nonfatal Serious Adverse Events

There were three SAEs in two patients: depression requiring hospitalization in one subject and hepatic cirrhosis and hepatic encephalopathy in another.

6.1.12.5 Adverse Events of Special Interest (AESI)

There were no reports of thromboemboli.

6.1.12.7 Dropouts and/or Discontinuations

There was no statistical impact on the single subject who discontinued late in the trial course.

6.1.13 Study Summary and Conclusions

This trial supplied information on the PK of the product as well as efficacy and safety. It was too small to address efficacy in the surgical patient subpopulation

6.2 Trial #2

GENA-08: *Clinical Study To Investigate The Efficacy, Safety, And Immunogenicity Of Human-cl rhFVIII In Previously Treated Patients With Severe Haemophilia A*

6.2.1 Objectives (Primary, Secondary, etc)

Primary: Test the efficacy of NUWIQ® in previously treated adult patients during prophylaxis, in the treatment of bleeding disorders and in surgical prophylaxis

Secondary:

- Calculate incremental recovery of FVIII:C
- Investigate the immunogenic potential of NUWIQ®
- Assess the safety of NUWIQ®

6.2.2 Design Overview

This was a prospective, open-label, international, multicenter, phase 3 trial in previously treated adult subjects with severe hemophilia-A. Subjects were treated at home with NUWIQ® for prophylaxis, treatment of BE and surgical prophylaxis, if required. In vivo recovery (IVR) was measured at Visit 1 and after 3 and 6 months.

Safety and immunogenicity were monitored at intervals throughout the trial.

6.2.3 Population

Identical to 6.1.3

6.2.4 Study Treatments or Agents Mandated by the Protocol

IVR was assessed at visit 1, at 3 months and at 6 months (visit 1 after at least 72 hour washout since last product infusion). At these three visits subjects received 50 IU per kg NUWIQ® for evaluation of IVR.

Patients being treated prophylactically were to receive 30–40 IU FVIII per kg every other day for 6 months and at least 50 EDs had been reached. Two dose escalations of +5 IU/kg each were allowed in case of an inadequate response (≥2 spontaneous BEs during one month).

Required units = body weight (kg) * desired FVIII rise (%) (IU/dL) * 0.5
[assuming that the recovery of FVIII is 2%/(IU/kg)]
The required target peak levels were:
• 40–60% in case of minor hemorrhage
• 60–80% in case of moderate to major hemorrhage
• 100–120% in case of major to life threatening BEs

The recommended dosages were identical to 6.1.4, Part II:

6.2.6 Sites and Centers

Austria (1 subject), Bulgaria (31 subjects), Germany (4 centers, 8 subjects), United Kingdom (5 centers, 15 subjects)

6.2.7 Surveillance/Monitoring

The Independent Data Monitoring Committee reviewed data at the end of the trial prior to close of the database. Monitoring was done by two contract review organizations in Bulgaria and the United Kingdom, and by Octapharma in Germany and Austria.

6.2.8 Endpoints and Criteria for Study Success

Prophylactic treatment:
Frequency of spontaneous breakthrough bleeds assessed after 50 ED and at the end of trial as:

- Excellent: <0.75 spontaneous bleeds per month
- Good: Between 0.75 and 1 spontaneous bleeds per month
- Moderate: Between 1 and 1.5 spontaneous bleeds per month
- Poor: >1.5 spontaneous bleeds per month

Study product consumption

Bleeding episodes:
Efficacy was assessed as:

- *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 8–12 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

All of the above were recorded by patients in a diary.

Surgical prophylaxis:
Intraoperative efficacy:

- *Excellent*: Intra-operative blood loss was lower than or equal to the average expected blood loss for the type of procedure performed in a patient with normal hemostasis and of the same sex, age, and stature.
- *Good*: Intra-operative blood loss was higher than average expected blood loss but lower or equal to the maximal expected blood loss for the type of procedure in a patient with normal hemostasis.
- *Moderate*: Intra-operative blood loss was higher than maximal expected blood loss for the type of procedure performed in a patient with normal hemostasis, but hemostasis was controlled.
- *None*: Hemostasis was uncontrolled necessitating a change in clotting factor replacement regimen.

Postoperative efficacy:

- *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 human-cl rhFVIII 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.

Immunogenicity was determined by the modified Bethesda assay (≤0.6 Bethesda units for low titer) at screening, before the first and second infusions, after 10-15 EDs, and at three months and at six months.

Safety was monitored by recording AEs throughout the trial, and measuring vital signs and routine safety laboratory parameters (measured by local laboratories) at pre-defined time points.

All 32 subjects were included in the prophylactic efficacy analysis.

Reviewer Comment: These endpoints were appropriate for this trial.

6.2.9 Statistical Considerations & Statistical Analysis Plan

The statistical analysis of all endpoints was exploratory; no confirmative statistical analysis was planned. Due to the limited number of patients, no stratification for any subgroup analyses was planned, except for subgroups of patients with BEs and those with surgeries.

Missing values were not replaced.

6.2.10.1 Populations Enrolled/Analyzed

32 subjects enrolled in the trial and were included in the safety and intention to treat populations. All 32 received prophylactic treatment (PROPH) but only 26 are included in the prophylaxis-per protocol population. Six subjects met pre-defined criteria for exclusion (five for >5 days between prophylactic doses and one for <50 ED).

6.2.10.1.1 Demographics

Table 8
Demographics

Mean Data (Range):	Intention to Treat	Per Protocol
Age	37.3 (18-75)	37.8 (18-75)
BMI	25.8 (17-37)	24.7 (17-31)
Race/Ethnicity		
Asian	3 (9.4%)	2 (7.7%)
White	29 (90.6%)	24 (92.3%)
Not Hispanic/ Latino	32(100%)	26 (100%)

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
As in 6.1.10.1.2

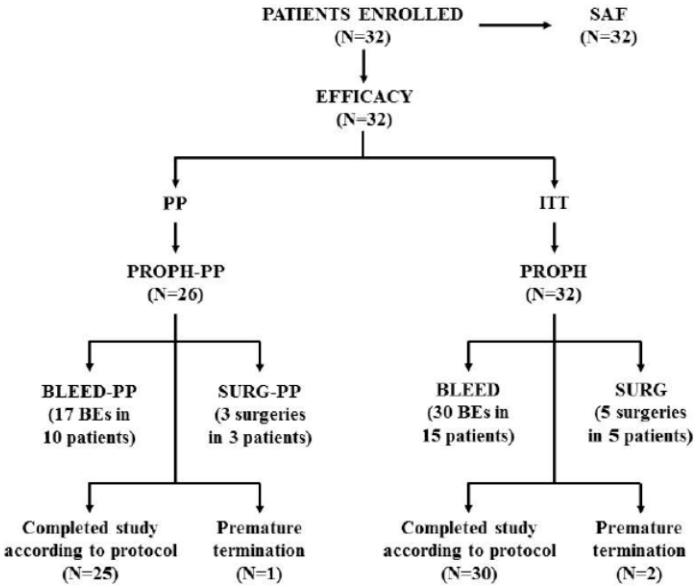
6.2.10.1.3 Subject Disposition
See 6.2.10.1

Thirty breakthrough BE occurred in 15 subjects. Seventeen of these BE were included in the BLEED-PP (per protocol) population. The remaining subjects were not in the PP population.

Surgery where at least one dose of NUWIQ® was administered happened on five occasions in five subjects. Three of these were in the PP population.

Two subjects terminated participation prematurely. One withdrew consent after 17 ED, one died after 76 ED from a seizure (deemed unrelated). Disposition of subjects from Trial GENA-08 is illustrated in Figure 2 below, reproduced from the application.

Figure 2
Subject Disposition



BE = bleeding episode; BLEED = study population of BEs treated with Human-cl rhFVIII; PROPH = study population of patients receiving prophylaxis; ITT = intention-to-treat; PP = per-protocol; SAF = study population of patients in safety analysis; SURG = study population of surgeries treated with Human-cl rhFVIII.
Source: Section 14, Tables 14.1.1.1, 14.2.8, 14.2.20.1 and 14.2.24.2; Appendix 16.2, Listings 16.2.1.1, 16.2.1.2 and 16.2.6.8.3.

Source: original BLA 12555/0; Section 5.3.5.2 Clinical Study Report p 43.

6.2.11 Efficacy Analyses

If the estimated ratio of annualized bleeding was less than 0.5 (i.e., greater than a 50% reduction) clinical importance of the individualized prophylaxis regimen will have been demonstrated. The safety endpoint with regard to inhibitors would be met if the upper one-sided 97.5% confidence limit was below 6.8%.

6.2.11.1 Analyses of Primary Endpoint(s)

Prophylaxis:
The mean number of BE during the prophylaxis period, excluding surgically-related, was 0.6 ± 1.2 per patient per month. The following compares historical BE rates in those

subjects who had been receiving prophylaxis prior to the trial (N=21). The remainder of subjects had only been receiving on demand treatment.

Table 9

Prophylactic dose (IU/kg/month) (historical)	Prophylactic dose (IU/kg/month) (study)	BE/month (historical)	BE/month (at end of study)
296.2	451.2	.540	.263

Subjective assessment of prophylactic efficacy:

Spontaneous BEs:	32 (100%)	
All types BE:	Excellent	29 (90.6%)
	Good	2 (6.3%)
	Moderate	1 (3.1%)
	Poor	0

Reviewer Comment: These data meet the criteria for prophylaxis efficacy.

Treatment of Bleeding:
There were 30 BE treated with at least one dose of NUWIQ® (versus 44 total BE) in 15 subjects. The remainder were minor and were untreated. Of the 30, 14 were spontaneous, 14 traumatic, and two "other". 60% involved the knee or ankle. Overall of the 30, 14 were rated as minor and 16 as moderate to major. There were no life-threatening BEs. Subjects rated efficacy as excellent (71.4%) or good (28.6%).The use of NUWIQ in the treatment of BE in this trial is delineated in Table 10, below.

Table 10

Parameter	Mean	SD	Median	Range
Number of EDs (for bleedings)*	1.60	1.55	1.00	1–8
Dose of Human-cl rhFVIII per BE, IU	5037.0	5824.2	4000.0	1500–24,000
Dose of Human-cl rhFVIII per BE, IU/kg	60.4	73.4	33.3	20–353
Number of dosages administered*	1.80	2.37	1.00	1–12
Dose of Human-cl rhFVIII per infusion, IU	2775.5	872.4	2500.0	1500–4000
Dose of Human-cl rhFVIII per infusion, IU/kg	33.3	6.7	32.1	20–53

* Dosage used to treat several simultaneous bleedings are counted only once in this analysis.
BE = bleeding episode; BLEED = study population of BEs treated with Human-cl rhFVIII; ED = exposure day; IU = international unit; SD = standard deviation.
Source: Section 14, Tables 14.2.13, 14.2.14 and 14.2.16.

Source: original BLA 12555/0; Section 5.3.3.2 Clinical Study Report p 51.

Reviewer Comment: These data support efficacy in treatment of BE and the dosing recommendations in the draft label

Surgical Prophylaxis:
Perioperative use of NUWIQ is detailed in Table 11, below. There were six surgical procedures. One was emergent (an emergency knee replacement following a traumatic injury) and treated with a different FVIII product (not specified), leaving one minor (tooth extraction) and four major operations (two arthroscopies, one hip replacement, one cholecystectomy/liver biopsy) in five subjects. Four subjects received a single preoperative loading dose; one received two - a level of 0.96 IU/mL was attained after one but local policy required a level of 1.0 IU/mL.

Blood loss was within the expected range for two operations. For two operations the reported blood loss (none) was less than the expected blood loss (20 and 500 mL) and for one surgery, although the actual blood loss (100 mL) was 50 mL greater than the average expected loss, it was significantly below the maximum expected blood loss for this type of procedure (600 mL).

Efficacy was related as excellent intraoperatively and overall. For one subject intraoperative efficacy was rated as good and overall (including the postoperative course) as moderate. This decrement in scoring may have been due to the development of three spontaneous minor nose bleeds postoperatively, not requiring treatment, but detracting from the intraoperative hemostasis. This subject is also the one who had more than expected blood loss intraoperatively.

Table 11
Surgical Prophylaxis

Parameter	Mean	SD	Median	Range
Total dose of Human-cl rhFVIII (IU)	37,680.0	32,711.4	25,000.0	8400–89,500
Total dose of Human-cl rhFVIII (IU/kg)	421.77	369.24	320.92	95.5–1028.7
Pre-operative loading dose (IU/kg)	49.61	6.58	50.00	39.2–57.5
Infusions after end of surgery (IU/kg)	372.16	366.74	269.58	45.5–971.3
Total dose of Human-cl rhFVIII per ED (IU/kg)	54.86	13.13	60.05	31.8–64.2
Dose of Human-cl rhFVIII per infusion (IU)	3104.06	341.16	3062.50	2777.8–3580.0
Dose of Human-cl rhFVIII per infusion (IU/kg)	35.06	4.36	35.66	30.0–41.1

ED = exposure day; IU = international unit; SD = standard deviation; SURG = study population of surgeries treated with Human-cl rhFVIII.
Source: Section 14, Tables 14.2.29, 14.2.30 and 14.2.32.

Source: original BLA 12555/0; Section 5.3.3.2Clinical Study Report p 58.

Reviewer Comment: These data support the indication of perioperative prophylaxis.

6.2.11.2 Analyses of Secondary Endpoints

Values of in vivo recovery (IVR) were consistent with prior studies (GENA-09 and GENA-04).

No FVIII inhibitors or non-inhibitory anti-FVIII antibodies were detected in any subject at any time point in the trial.

See 6.2.12 for safety data.

Reviewer comment: Analysis of the primary and secondary outcome data indicate that Human-cl rhFVIII is efficacious as prophylaxis, for the treatment of BEs and for prophylaxis during surgical procedures. Please note again the limitations of the data considering there were only 5 surgeries treated with the product

6.2.11.3 Subpopulation Analyses

Due to the limited number of subjects, no subgroup analyses were planned, other than those with BE and those with surgery.

6.2.11.4 Dropouts and/or Discontinuations

There were no significant missing data.

6.2.12 Safety Analyses

6.2.12.1 Methods

Subject reports of AEs were solicited at all subject visits. Patient diaries were not used.

6.2.12.2 Overview of Adverse Events

AEs were documented in 66% of subjects, but after only 1.9% of all infusions. Of the 65 AEs, 91% were mild or moderate.

Five AEs were assessed as possibly related to NUWIQ® infusion. Two were injection site reactions (after first and 15th infusion). These are recognized as a possible risk of FVIII preparations. The remaining three (vertigo, dry mouth and paresthesia) all occurred in a single subject with the first infusion. None recurred during the subsequent 95 ED of prophylactic treatment. All five AEs were mild, non-serious and resolved without sequelae. No AE (save the single death) led to discontinuation of the trial or the drug.

AE occurring in >5% of subjects were abdominal pain (28% of subjects), diarrhea (6.3%), nausea (6.3%), fever (6.3%), nasopharyngitis (9.4%), contusion (6.3%), back pain (6.3%), headache (9.4%), paresthesia (6.3%), epistaxis (6.3%).

The Independent Data Monitoring Committee reviewed the safety data and was unanimous that the trial was safe and that the clinical program could continue.

6.2.12.3 Deaths

One subject with a chronic seizure disorder died after status epilepticus that was assessed as not related to the investigational product.

6.2.12.4 Nonfatal Serious Adverse Events

There were four SAEs, two rated as serious. One subject died following a protracted seizure. These six SAEs could all be explained by an accident or the patient's medical history. None were deemed related to NUWIQ®.

6.2.12.5 Adverse Events of Special Interest (AESI)

There were no reports of thromboemboli.

6.2.12.6 Clinical Test Results

No abnormalities were considered clinically relevant.

6.2.12.7 Dropouts and/or Discontinuations

There was no impact on this trial of subject discontinuations.

6.2.13 Study Summary and Conclusions

The results from this trial demonstrate favorable safety and tolerability of NUWIQ® in this patient population for the indications of prophylaxis, for the treatment of BEs and for perioperative care.

6.3 Trial #3

GENA-03: *Prospective clinical study in children with severe haemophilia A to investigate clinical efficacy, immunogenicity, pharmacokinetics, and safety of Human-cl rhFVIII*

6.3.1 Objectives (Primary, Secondary, etc)

Primary:
To assess clinical **efficacy** of *Human-cl rhFVIII* in prevention and treatment of (breakthrough) bleeding episodes in children

Secondary:

- Determine **pharmacokinetics** in age groups 2-5 and 6-12 years
- Determine **incremental recovery** of NUWIQ®
- Investigate **immunogenic potential** of NUWIQ®
- Assess **efficacy in surgeries**
- Assess **safety**

6.3.2 Design Overview

This was a prospective, non-controlled, open label, multinational, multicenter phase 3

trial in 59 children with severe hemophilia A (FVIII <1%), aged 2 to 5 and 6 to 12 years all with at least 50 previous exposure days (EDs) to FVIII concentrates. In phase I PK characteristics were determined in a subset of subjects in a non-randomized crossover design with their previous FVIII product. Phase II was an open label treatment phase continuing for six months.

6.3.3 Population

Identical to 6.1.3, except age 2 to12 years, and prior ED ≥50 (not 150, to account for shorter duration of disease).

6.3.4 Study Treatments or Agents Mandated by the Protocol

PK (Phase I): 50 IU per kg of NUWIQ® and the previously used FVIII product, in a crossover design, following at least a 72 washout after the most recent FVIII exposure. IVR was determined at the beginning of phase II (non-PK subjects), and at three and six months for all subjects.

Prophylactic treatment: 30-40 IU either every other day or three times per week (to maintain the child's prior routine). Two dose escalations of each +5 IU FVIII/kg BW were allowed in case of an inadequate response (≥2 spontaneous BEs within one month).

Breakthrough BE: Identical to 6.1.4

Surgical Prophylaxis: Identical to 6.1.4

Reviewer Comment: No alterations were made for potential pharmacokinetic differences in children.

6.3.5 Directions for Use

6.3.6 Sites and Centers

United Kingdom (2), Czech Republic (1), Poland (3), Russian Federation (1), Turkey (5), France (2), Romania (1)

6.3.7 Surveillance/Monitoring

Follow-up visits were scheduled after 10 to 15 EDs (Interim Visit 1), at 3 months (±2 weeks), after 50 EDs (Interim Visit 2) and at 6 months (±2 weeks). At every study visit, subjects were tested for FVIII inhibitors and antibodies. Monthly compliance checks were to take place either by telephone or by a personal visit on the part of the patient in order to check whether the patient followed the every-other-day or 3-times-weekly treatment regimen and whether the given dose was adequate.

An interim analysis was conducted after 50 ED for 20 subjects, including10 below six years of age

6.3.8 Endpoints and Criteria for Study Success

See 6.2.8.

6.3.9 Statistical Considerations & Statistical Analysis Plan

The statistical analyses of all endpoints were exploratory; no confirmative statistical analyses were planned. All subjects who received at least one dose were included, and any who had data collected post-treatment were in the intention to treat group.

6.3.10 Study Population and Disposition

6.3.10.1 Populations Enrolled/Analyzed

PK Phase (Phase 1): 27 subjects, 13 2 to 5 years of age, 14 subjects 6 to 12 years of age
Prophylaxis (Phase 2): All subjects from Phase I plus 32 additional subjects, 16 in each age group

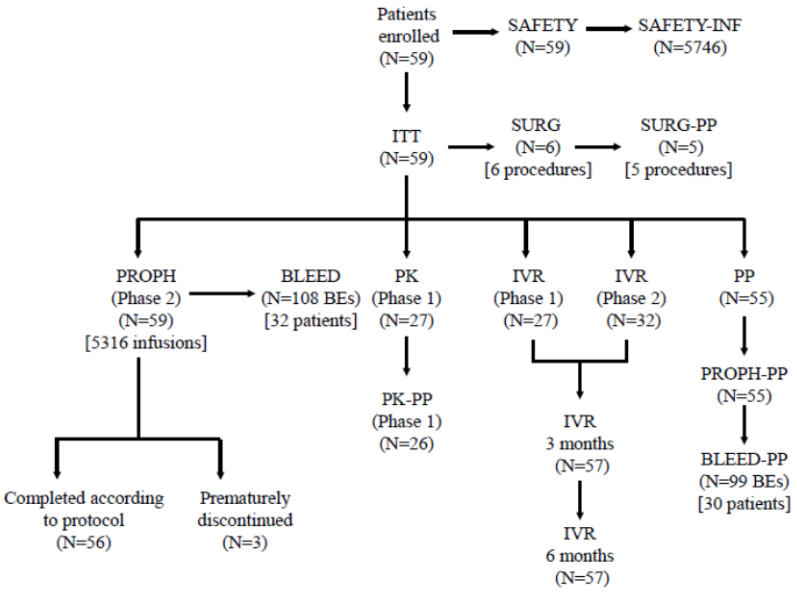
6.3.10.1.1 Demographics

Age (Mean):	6.1 ± 2.97
Weight:	26.7 ± 12.3
Race:	All subjects were white and non-Hispanic/non-Latino.
Country:	Poland (24), United Kingdom (10), Russian Federation (9), Turkey (9), Romania (3), Czech Republic (2), France (2)

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

6.3.10.1.3 Subject Disposition
Disposition of subjects in GENA-03 is summarized in Figure 3 below, reproduced from the application.

Figure 3
Subject Disposition



BLEED = study population of BEs treated with *Human-cl rhFVIII*; PROPH = study population of patients receiving prophylaxis; ITT = intention-to-treat; IVR = in vivo recovery; PK = pharmacokinetics; PP = per-protocol; SAFETY = study population of patients in safety analysis; SAFETY-INF = all infusions within safety population; SURG = study population of surgeries treated with *Human-cl rhFVIII*.
Source: Section 14, Tables 14.1.1.1, 14.1.1.2, 14.1.1.3, 14.2.6.1, 14.2.31.1.1 and 14.3.1.2; Appendix 16.2, Listing 16.2.6.8.3

Source: original BLA 12555/0; Section 5.3.5.2 Clinical Study Report p 59.

Reasons for exclusion from the prophylaxis-per protocol population (N=4) were <50 ED (2), prolonged interval between prophylactic doses (1) and use of another FVIII product (1 – diagnosed with vonWillebrand disease, treated with vonWillebrand containing factor and subsequently dropped from the trial).

6.3.11 Efficacy Analyses

6.3.11.1 Analyses of Primary Endpoint(s)

Efficacy

- 20 subjects (34%) in the prophylaxis group experienced no BE and 14 (24%) experienced a single BE during the trial
- Efficacy for traumatic BE was excellent (93%), good (5.1%) and poor in 1 subject.
- Overall BE efficacy was excellent in 84%, good in 9%, moderate in 5% and poor in 3%.
- There was no difference in efficacy between the two age cohorts.
- The monthly rate of BE during the prophylaxis period was 0.123 (spontaneous), and 0.192 (traumatic) and the rates were higher for the older age group
- The mean daily dose was 38.9 IU/kg

- Mean monthly dose was 519 IU per kg versus historical value of 504 IU per kg. The monthly overall BE rate was approximately 15% lower than the historical comparison.

Reviewer Comment: 38.9 IU/kg is near the upper range of the 30-40 IU per kg dose. This is due in part to the fact that doses were generally rounded up to whole vials. Only 500 IU vials were available. 250 IU vials will also be available when the product is licensed. However, a difference due to PK differences was not addressed or excluded.

Treatment of Breakthrough BE

- 108 BE in 32 subjects
  - 60% traumatic, 33% spontaneous, 7% "other"
  - 57% minor, 43% moderate to major, one unknown
  - The modal number of treated BE during the trial was one
- The mean dose of NUWIQ® was 44 IU per kg for minor BE and 46 IU per kg for moderate to major BE
- 69% were treated with a single infusion; 81% with one to two
  - 6% required three infusions, 4% required four, two each required 5,6 or 8 and one each required 12, 15 or 22 infusions
- Efficacy ratings for minor BE were 87% excellent, 11% good and one subject moderate
- Efficacy ratings for moderate to severe BE were 50% excellent, 11% good, 35% moderate and 4% none.
  - Two subjects had BE rated as "none". Both had additional BE that were treated with NUWIQ with efficacy rated as moderate to excellent.

Reviewer Comment: 44 and 46 IU per kg is slightly above the protocol recommended dose of 20-30 IU per kg for minor bleeding and 30-40 IU per kg for moderate-major bleeding. Again, this could be due to rounding up to the next vial.

Surgery

- Six planned operations: port catheter (re)placement (5) and circumcision (1)
  - Efficacy rating by both hematologists and surgeons as excellent in all
- All received 50 IU per kg loading dose prior to surgery
- Blood loss 2-10 mL

Reviewer Comment: Although all rated as "major", these surgical procedures were all relatively minor without major expected blood loss. Thus efficacy in what others might consider major surgery has not been specifically demonstrated in this population.

6.3.11.2 Analyses of Secondary Endpoints

PK

Table 12

Parameter	Prior FVIII	NUWIQ®	NUWIQ® Adult value (from GENA-01)
AUCnorm (h x IU/mL/(IU/kg)	0.24±0.09	0.23±0.08	0.39±0.14

Cmax (IU/mL)	0.828±0.269	1.004±0.186	N/A
Cmax norm (IU/mL/(IU/kg)	0.019	0.019	0.25±0.004
IVR (%IU/kg)	1.848±0.457	1.876±0.354	2.5±0.37
T1/2 (h)	11.04±2.50	9.73±2.69	14.73±9.96
CL (mL/h/kg)	4.76±1.90	4.89±1.95	2.94±1.18
Vss (mL/kg)	60.35±13.79	54.9±11.21	49.58±17.27

Mean ± SD. Data reported for CHR assay. Results were similar for the OS assay.

Reviewer Comment: There were no differences between the age groups and no changes with time through the six months of the trial. There are some differences in PK data between the pediatric and adult populations that are typical of differences in drug distribution and metabolism is children. Specifically clearance was higher in children as was volume of distribution. This may require a different dosing schedule for pediatric patients.

Immunogenicity
No FVIII inhibitors were detected. In two subjects a low titer non-inhibitory, non-neutralizing anti-FVIII antibody was present prior to first exposure and did not affect efficacy.

Surgery
See 6.3.11.1

Safety

6.3.11.3 Subpopulation Analyses

There was no attempt at subpopulation analysis except by age (2-5 and 6-12 years), bleeding severity and operation severity. There was no attempt at analysis by study center.

6.3.11.4 Dropouts and/or Discontinuations

Missing data were not replaced.
A single subject was removed from the trial after a diagnosis of vonWillebrand disease.
Missing data were uncommon and did not affect the conclusions of the trial.

6.3.12 Safety Analyses

6.3.12.1 Methods

The trial documented AEs by means of patient diaries.

6.3.12.2 Overview of Adverse Events

124 treatment-emergent AE

- 38/59 subjects
- 80% mild, 20% moderate
- Two were assessed as possibly related: one back pain after 2 ED and 1 headache

- Most AE reported only once and many represent AE typically found in a pediatric population (refer to Table 13 below reproduced from the application). AE typical of a hemophilia population were uncommon.
- Seven SAE in five subjects
    - Infected port catheter, hospitalization for mild head trauma (2), acute tonsillitis (three SAE in one subject)
- Data Monitoring Committee reclassified six originally assessed by investigators as unrelated to possibly related due temporal association with an infusion [chills (3), rash (3)]

Source: original BLA 12555/0; Section 5.3.3.2Clinical Study Report p 102

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Table 13
AE Occurring in >1 subject

Primary SOC PT	No. of patients (% of SAF)	No. of infusions (% of Safety-INF)
Any SOC*	38 (64.4)	109 (1.9)
General disorders and administration site conditions	*7 (11.9)*	*11 (0.2)*
Chills	4 (6.8)	4 (<0.1)
Pyrexia	5 (8.5)	6 (0.1)
Infections and infestations	*20 (33.9)*	*39 (0.7)*
Bronchitis	2 (3.4)	2 (<0.1)
Ear infection	2 (3.4)	2 (<0.1)
Nasopharyngitis	6 (10.2)	7 (0.1)
Otitis media	2 (3.4)	2 (<0.1)
Pharyngitis	2 (3.4)	2 (<0.1)
Rhinitis	6 (10.2)	6 (0.1)
Tonsillitis	2 (3.4)	4 (<0.1)
Upper respiratory tract infection	2 (3.4)	3 (<0.1)
Varicella	3 (5.1)	3 (<0.1)
Injury, poisoning, procedural complications	*14 (23.7)*	*20 (0.3)*
Head injury	3 (5.1)	3 (<0.1)
Injury	5 (8.5)	6 (0.1)
Joint injury	2 (3.4)	2 (<0.1)
Limb injury	2 (3.4)	2 (<0.1)
Musculoskeletal and connective tissue disorders	*5 (8.5)*	*9 (0.2)*
Arthralgia	2 (3.4)	2 (<0.1)
Back pain	2 (3.4)	2 (<0.1)
Pain in extremity	2 (3.4)	3 (<0.1)
Nervous system disorders	*4 (6.8)*	*5 (<0.1)*
Headache	4 (6.8)	5 (<0.1)
Respiratory, thoracic and mediastinal disorders	*6 (10.2)*	*9 (0.2)*
Cough	5 (8.5)	7 (0.1)
Skin and subcutaneous tissue disorders	*6 (10.2)*	*7 (0.1)*
Rash	4 (6.8)	5 (<0.1)

*Patients with more than one PT within a SOC were only counted once for this SOC.
AE = adverse event; PT = preferred term; SAFETY = study population of patients in safety analysis; Safety-INF = study population of *Human-cl rhFVIII* infusions administered to patients in the safety analysis population; SOC = system organ class.
Source: Section 14, Table 14.3.1.5

Source: original BLA 12555/0; Section 5.3.3.2Clinical Study Report p 103.

Reviewer Comment: These data support the safety of NUWIQ in children 2-12 years of age.

6.3.12.3 Deaths

There were no deaths in this trial.

6.3.12.4 Nonfatal Serious Adverse Events

See 6.3.12.2

6.3.12.5 Adverse Events of Special Interest (AESI)

There were no reports of thromboemboli.

6.3.12.6 Clinical Test Results

6.3.12.7 Dropouts and/or Discontinuations

No subjects discontinued due to AE.

6.3.13 Study Summary and Conclusions

This trial showed that NUWIQ® is safe and effective for use in children 2-12 years of age. There were no major differences between the 2-5 and 6-12 year old groups or PK data between NUWIQ® and previously used FVIII products. There were some PK differences with adult data from trial GENA-01.

7. Integrated Overview of Efficacy

7.1 Indication #1

Control and prevention of bleeding episodes in adults and children with Hemophilia A

7.1.1 Methods of Integration

Data from the three pivotal trials, GENA-01, -03 and 08 were used for an integrated analysis of efficacy. GENA-03 and -08 had efficacy as the primary outcome. Data from the non-IND studies GENA-09 and -04 are supportive.

7.1.2 Demographics and Baseline Characteristics

In total 54 adult and 59 pediatric (age 2-12) subjects were included in these studies. All had severe hemophilia (FVIII:C<1%).

7.1.4 Analysis of Primary Endpoint(s)

Prevention
95 subjects received every other day (or three per week) prophylaxis in GENA-03 and -08. An additional 18 received prophylaxis in GENA-09 and -04. Between 36% and 56% of subjects had no BE, and few had >5. Overall prophylactic efficacy was excellent in 82-100% of subjects, good in 1.7 to 9.1%, moderate in 3.4 to 9.1%, and poor in none. In response to a request by FDA, the annualized bleeding rate in GENA-01 was determined to be more than twice that in GENA-08 and -03. These data confirm the efficacy of prophylaxis with NUWIQ® in adults and children with hemophilia.

Control of Bleeding
The mean number of infusions ranged from 1 to 1.5 (range 1-22) with mean doses of 32-45 IU per kg. The highest dose was in the pediatric population. For adults only the mean doses were 32-35 IU per kg per infusion. Overall efficacy in the three IND studies 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 than moderate to major BE.

Reviewer Comment: The higher dose in the pediatric population may be due in part to rounding up to the next vial size, but a disparity due to PK differences could not be excluded.

7.1.11 Efficacy Conclusions

These data confirm the efficacy of prophylaxis with NUWIQ® in adults and children with hemophilia.

7.2 Indication #2

Perioperative management in adults and children with hemophilia-A

7.2.1 Methods of Integration

Overall there were 34 surgical procedures in 20 subjects; 20 (in seven subjects) minor and 14 (in 13 subjects) moderate to major.

7.2.4 Analysis of Primary Endpoint(s)

The odds of a successful treatment ≥70% were 84 to >99.9% for all operations and 64 to 99.8% for major operations. The doses ranged from 35 IU per kg to 50 IU per kg. In general higher doses were used for children.

7.2.5 Analysis of Secondary Endpoint(s)

7.2.6 Other Endpoints

7.2.7 Subpopulations

7.2.8 Persistence of Efficacy

No conclusions could be drawn about the relationship of efficacy to duration of therapy. However efficacy was generally high for all operations.

7.2.9 Product-Product Interactions

7.2.10 Additional Efficacy Issues/Analyses

7.2.11 Efficacy Conclusions

These doses are in line with the recommendations for frequency of dosing and duration of therapy in the European Medicines Agency (EMA) Core Summary of Product Characteristics (SPC) for human plasma-derived FVIII and recombinant FVIII (rFVIII) products, which are applicable to *Human-cl rhFVII.*

The outcomes of the trial support the efficacy of NUWIQ® in children and adults with hemophilia A for control and prevention of perioperative bleeding.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The safety concerns for this product are hypersensitivity and allergic reactions, thromboembolic events, and inhibitor development. 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.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

135 subjects participated in four studies (GENA-01, -03, -08 and -09). 18 subjects in GENA-09 participated in the extension trial GENA-04. Subjects received 1835 to 6289 IU per kg with a mean of 55 to 228 infusions over a mean of 53 to 226 ED.

8.2.3 Categorization of Adverse Events

All serious and non-serious adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

The subjects in the two supportive non-IND trials were done at a single Russian center in a chronically undertreated population.

8.4 Safety Results

8.4.1 Deaths

There was a single death (GENA-08) following status epilepticus, deemed unrelated to NUWIQ®.

8.4.2 Nonfatal Serious Adverse Events

There were 11 AE in eight subjects in the three of the eight studies. These are delineated in Table 14.

Table 14
SAEs

Study	Subject	AE	Outcome	Causality
GENA-01	1	Depression, suicidal	Recovered/resolved	Not related
	2	Hepatic encephalopathy	Recovered/resolved	Not related
	2	Hepatic cirrhosis	Nor recovered/resolved	Not related
GENA-08	3	Traumatic fracture	Recovered/resolved	Not related
GENA-03	4	Device-related infection	Recovered/resolved	Not related
	5	Head injury	Recovered/resolved	Not related
	6	Head injury	Recovered/resolved	Not related
	7	Acute tonsillitis	Recovered/resolved	Not related
	7	Upper respiratory infection	Recovered/resolved	Not related
	7	Lower respiratory infection	Recovered/resolved	Not related
	8	Hemarthrosis	Recovered/resolved	Not related

8.4.4 Common Adverse Events

A total of 272 AE in 79 subjects were reported. The most commonly affected System Organ Class was infections and infestations (57 subjects). Most were in pediatric subjects and reflected common childhood illnesses.

8.4.8 Adverse Events of Special Interest

There were no reports of the development of FVIII inhibitors or non-neutralizing anti-FVIII antibodies, or thromboemboli.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

AE were not related to dose or duration of treatment.

8.5.8 Immunogenicity (Safety)

No subject developed inhibitors or non-neutralizing anti-FVIII antibodies

8.6 Safety Conclusions

The safety profile of NUWIQ® has been adequately demonstrated for the proposed population and indications.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Hemophilia-A occurs almost exclusively in males. No females were included in any of the trials.

9.1.3 Pediatric Use and PREA Considerations

PREA is triggered. Trial GENA-03 was a pediatric trial and would suffice for approval for use in children.

In 59 pediatric patients (2-12 years of age) with severe hemophilia prophylactic treatment was rated as excellent or good in 97% of subjects and efficacy in treating bleeding episodes was rated as excellent or good in 82% of episodes, despite the 62% incidence of traumatic bleeding in this pediatric population. There was no difference in treatment response between the 2-5 and 6-12 year old age groups. Perioperative efficacy was also demonstrated in these pediatric groups.

9.1.5 Geriatric Use
Subjects >65 years of age were not studied.

10. CONCLUSIONS

There were no safety signals identified during the clinical trials for NUWIQ®. The clinical development program included 135 treated subjects and no confirmed inhibitor development, severe allergic reactions, thrombotic events, or other unexpected events were observed. Based on my review of the submitted, data NUWIQ® appears safe and efficacious in child and adult patients with hemophilia A. An approval is recommended.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 15
Risk Benefit Considerations for NUWIQ®

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Hemophilia A is a hereditary bleeding disorder characterized by recurrent and potentially life threatening bleeding. If left untreated, bleeds lead to chronic arthropathy, muscular atrophy and deformities. • Treatment of bleeds may delay these complications, but does not prevent it. • Primary prophylaxis with regular FVIII injections initiated at an early age is becoming the standard of care	• Hemophilia A is a hereditary, life-threatening disease • Hemophilia A can have a debilitating impact on physical and psychosocial well being
Unmet Medical Need	The induction of inhibitors, thromboembolic phenomena, allergic phenomena, and the potential for transmission of known and currently unknown blood-borne pathogens are all potential complications of exogenous FVIII.	These complications are potentially lessened in this recombinant product produced in a human cell line with human post-translational modification and no animal product used.
Clinical Benefit	Three pivotal trials were submitted, one of which was a pediatric trial pediatric trial. All subjects had severe hemophilia and had been previously treated with a factor VIII product. Efficacy was demonstrated for the treatment of acute bleeds, perioperative management, and routine prophylaxis. No new safety concerns were identified.	• The evidence for clinical benefit is compelling.
Risk	• The most substantial risks of treatment with NUWIQ® are allergic reactions and development of FVIII inhibitors. No confirmed inhibitors or significant allergic reactions were noted during the trial; however, the study may have been underpowered to adequately identify these potential risks. • No serious adverse events were found to be attributable to NUWIQ®. • No other safety signals were apparent	• All evidence indicates that NUWIQ® is well tolerated and safe.
Risk Management	• The most substantial risks of treatment with NUWIQ® are allergic reactions and development of FVIII inhibitors. • No other safety signals were apparent.	• If NUWIQ® were approved, routine measures, such as the package insert and the current pharmacovigilance plan, would be adequate to manage the risks

11.2 Risk-Benefit Summary and Assessment

The efficacy of NUWIQ® has been established for control and prevention of bleeding episodes, perioperative management and routine prophylaxis to prevent or reduce the frequency of bleeding episodes in clinical studies in adults and in children from 2-12 years old. NUWIQ® is prepared from a human cell line and has potential advantages in decreased inhibitor formation and hypersensitivity reactions. Although no subjects developed neutralizing antibodies to FVIII in the pivotal clinical trial, the potential for developing inhibitors is discussed in the Warnings and Precautions section of the Package Insert. No serious adverse events were found to be attributable to NUWIQ®.

11.3 Discussion of Regulatory Options

The identification and characterization of risk factors for inhibitor formation require an improved understanding of how patient-specific and treatment-related factors work together to influence inhibitory antibody production. Pre-market studies are limited in their ability to identify risk factors because most studies are underpowered and are limited to only previously treated patients who do not have a history of inhibitor formation. The larger hemophilia community that will be exposed to the product after licensure, including minimally treated and previously untreated patients as well as patients undergoing surgery and/or switching regimens, are often not included in pre-market studies. Large prospective post-marketing surveillance studies that include the patient population at large and designed to actively monitor and evaluate the risk factors for inhibitors are important for further characterization of the risk of inhibitor formation. The submitted Pharmacovigilance Plan is sufficient to address these important potential risks.

11.4 Recommendations on Regulatory Actions

This clinical reviewer recommends approval of this BLA. Efficacy and safety clinical data for NUWIQ® were found adequate to make a favorable benefit/risk determination and to support approval for the proposed indications of:
• Control and prevention of bleeding episodes,
• Perioperative management,
• Routine prophylaxis to prevent or reduce the frequency of bleeding episodes.

However, this reviewer notes that on the submitted draft label a specific indication for prophylaxis is not requested (in distinction to an indication for prevention, which is requested).

11.5 Labeling Review and Recommendations

Octapharma requested a proprietary name review for the tradename NUWIQ®. The proposed proprietary name was determined to be acceptable. The review of the label is ongoing and will be further discussed in an addendum to this review memo.

11.6 Recommendations on Postmarketing Actions

The proposed postmarketing pharmacovigilance studies (4.6) are deemed adequate.

6.x.11 Efficacy Analyses

6.x.12 Safety Analyses