

Application Type	Original BLA
STN	125555/0
CBER Received Date	June 5, 2014
PDUFA Goal Date	September 4, 2015
Division / Office	DB/OBE
Committee Chair	Andrey Sarafanov, PhD
Clinical Reviewer(s)	Victor Baum, MD
Project Manager	Jiahua Qian, PhD
Priority Review	No
Reviewer Name(s)	Min (Annie) Lin, PhD
Review Completion Date / Stamped Date	
Supervisory Concurrence	Renée Rees, PhD, Team Leader, Therapeutics Evaluation Branch
	Boguang Zhen, PhD, Branch Chief, Therapeutics Evaluation Branch
	Estelle Russek-Cohen, PhD, Director, Division of Biostatistics
Applicant	OCTAPHARMA
Established Name	Antihemophilic Factor (Recombinant) plasma/albumin free
(Proposed) Trade Name	Nuwiq
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	
Dosage Form(s) and Route(s) of Administration	Powder & solvent for solution for injection
Dosing Regimen	The required dosage is determined using the following formula: Required IU = body weight (kg) x desired FVIII rise (%) (IU/dL) x 0.5 (IU/kg per IU/dL)
Indication(s) and Intended Population(s)	For on-demand treatment and control of bleeding episodes, perioperative management of bleeding, and routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children with Hemophilia A

Table of Contents

Glossary	4
1. Executive Summary	5
2. Clinical and Regulatory Background.....	6
2.1 Disease or Health-Related Condition(s) Studied	6
2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s).....	6
2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission	7
3. Submission Quality and Good Clinical Practices	8
3.1 Submission Quality and Completeness.....	8
5. Sources of Clinical Data and Other Information Considered in the Review	8
5.1 Review Strategy	8
5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review	8
5.3 Table of Studies/Clinical Trials	9
6. Discussion of Individual Studies/Clinical Trials	10
6.1 Study GENA-01	10
6.1.1 Objectives (Primary, Secondary, etc.)	10
6.1.2 Design Overview	11
6.1.3 Population	11
6.1.4 Study Treatments or Agents Mandated by the Protocol	12
6.1.6 Sites and Centers.....	12
6.1.8 Endpoints and Criteria for Study Success.....	12
6.1.9 Statistical Considerations & Statistical Analysis Plan.....	13
6.1.10 Study Population and Disposition.....	14
6.1.11 Efficacy Analyses	14
6.1.12 Safety Analyses.....	16
6.2 Study GENA-08	16
6.2.1 Objectives (Primary, Secondary, etc.)	16
6.2.2 Design Overview	17
6.2.3 Population	17
6.2.4 Study Treatments or Agents Mandated by the Protocol	17
6.2.6 Sites and Centers.....	18
6.2.8 Endpoints and Criteria for Study Success.....	18
6.2.9 Statistical Considerations & Statistical Analysis Plan.....	19
6.2.10 Study Population and Disposition.....	20
6.2.11 Efficacy Analyses	20
6.2.12 Safety Analyses.....	21
6.3 Study GENA-03	22
6.3.1 Objectives (Primary, Secondary, etc.)	22

6.3.2 Design Overview	22
6.3.3 Population	23
6.3.4 Study Treatments or Agents Mandated by the Protocol	23
6.3.6 Sites and Centers.....	24
6.3.8 Endpoints and Criteria for Study Success.....	24
6.3.9 Statistical Considerations & Statistical Analysis Plan.....	24
6.3.10 Study Population and Disposition.....	25
6.3.11 Efficacy Analyses	26
6.3.12 Safety Analyses.....	27
7. Integrated Overview of Efficacy.....	27
7.1 Perioperative Management.....	28
7.1.1 Methods of Integration.....	28
7.1.4 Analysis of Primary Endpoint(s)	29
7.1.11 Efficacy Conclusions	30
10. Conclusions.....	30
10.1 Statistical Issues and Collective Evidence.....	30
10.2 Conclusions and Recommendations.....	31

GLOSSARY

ABR	Annualized bleeding rate
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BDD	B-domain-deleted
BE	Bleeding episode
BLA	Biologics license application
BW	Body weight
BU	Bethesda Units
CBER	Center for Biologics Evaluation and Research
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
ED	Exposure day
EMA	European Medicines Agency
FDA	Food and Drug Administration
FVIII	Blood coagulation factor VIII
FVIII:C	FVIII coagulant activity
HEK	Human embryonic kidney
ITT	Intention-to-treat
IU	International units
IVR	In vivo recovery
PK	Pharmacokinetic
PP	Per-protocol
PI	Package insert
PTP	Previously treated patient
rFVIII	Recombinant FVIII
SAE	Serious adverse event
SD	Standard deviation
VWD	von Willebrand disease

1. EXECUTIVE SUMMARY

The applicant submitted an original Biologics License Application (BLA) for *Human-cl rhFVIII* [Antihemophilic Factor (Recombinant), plasma/albumin free] for the control and prevention of bleeding episodes (also during and after surgery) in adults and children with Hemophilia A. *Human-cl rhFVIII* was developed by the applicant with the intention to provide a new rFVIII from a human cell line that is potentially less immunogenic for the treatment of hemophilia A.

There are six clinical studies in this BLA application, in which three studies (GENA-01, GENA-08 and GENA-03) are considered the pivotal studies for this submission. Two studies (GENA-09 and its extension GENA-04) are included as supportive studies. One study (GENA-11) was an extension study of pivotal trial GENA-01. Of the three pivotal trials, Study GENA-01 was a prospective, randomized, actively controlled, open-label cross-over, multicenter Phase 2 study. The proportion of bleeding episodes (BEs) with successful treatment in this study was 94.4%, with a 95% confidence interval (CI) of 92.8%, 95.8%. As the lower confidence limit for the rate of successfully treated BEs was greater than a pre-specified margin of 70% for success, the result supports the claim for on-demand treatment with *Human-cl rhFVIII*. The mean annualized bleeding rate (ABR) was 58.08 with a 95% CI of 44.43, 71.73.

The other two pivotal studies (GENA-08 and GENA-03) were non-controlled, single-arm trials conducted outside of the US and with no formal hypothesis testing planned within the studies. In Study GENA-08, a total of 44 BEs occurred in 16 (50%) out of 32 enrolled subjects during the prophylactic treatment. The mean ABR was 2.28 with a 95% CI of 0.94, 3.63. A significant reduction of 96% in mean ABR was observed when compared to the on-demand data in GENA-01 using a negative binomial regression model.

Study GENA-03 was a pediatric study with subjects 2-13 years old. A total of 129 BEs were experienced by 39 subjects and 20 subjects did not experience any BEs during the prophylactic treatment. The mean ABR was 4.12 with a 95% CI of 2.76, 5.48. Similarly, a significant reduction of 93% in mean ABR was obtained when compared to the on-demand data from GENA-01 using a negative binomial regression model.

The results from both studies (GENA-08 and GENA-03) support the claim for prophylactic treatment with *Human-cl rhFVIII* in both adult and children subjects with Hemophilia A.

No cases of thromboembolism were observed and no FVIII inhibitors were detected in any of the three pivotal studies. One death occurred during Study GENA-08 and was deemed unrelated to study treatment.

Surgical prophylaxis with *Human-cl rhFVIII* was demonstrated via an integrated analysis of pooled surgical interventions of subjects from five GENA studies: GENA-01, GENA-08, GENA-03, GENA-09 and GENA-04. Overall 94.1% (32/34) of surgical prophylaxis

were rated “Excellent” or “Good”, providing evidence of surgical prophylaxis with *Human-cl rhFVIII*.

There are no statistical concerns regarding efficacy and safety in this submission.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Hemophilia A is an inherited sex-linked disorder of blood coagulation in which affected males do not produce functional coagulation factor VIII (FVIII) in sufficient quantities to achieve satisfactory hemostasis. Subjects with hemophilia A are predisposed to recurrent BEs. Without adequate treatment these repeated hemarthroses and hematomas lead to long-term sequelae with severe disability. Subjects with hemophilia A are at high risk of developing major and life-threatening bleeds after surgical procedures.

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

The development of cryoprecipitate and subsequently FVIII concentrates, obtained by fractionation of human plasma, provided replacement FVIII and greatly improved clinical management and life expectancy of subjects with hemophilia A. However, there are concerns about virus transmissions by plasma-derived coagulation factor concentrates. Hamster cells have been used for the expression of commercial recombinant FVIII (rFVIII) concentrates. The use of non-human cell lines however raises the possibility of different contaminants and altered immunogenic potential. As the B-domain is dispensable for FVIII coagulation activity, B-domain-deleted (BDD) FVIII products have been used successfully to treat and prevent BEs in hemophilia A subjects.

Prophylaxis with FVIII concentrates is currently the preferred treatment regimen for subjects with severe hemophilia A, especially in very young subjects. However, on-demand treatment is still the predominant replacement approach in many countries.

The most serious complication in the treatment of hemophilia A is the development of neutralizing antibodies (inhibitors) against FVIII, rendering the patient resistant to replacement therapy and thereby increasing the risk of unmanageable bleeding. The use of a human cell-line for the expression of rFVIII is expected to provide a more genuine human glycosylation pattern than achieved with hamster cell-lines, which may result in an improved function and reduced immunogenicity.

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

Human-cl rhFVIII, with the trade name of Nuwiiq[®], has been approved for marketing in Germany for the treatment and prophylaxis of bleeding in all age groups with hemophilia A since August, 2014.

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

Human-cl rhFVIII [Antihemophilic Factor (Recombinant), plasma/albumin free] was developed by the applicant with the intention to provide a new rFVIII from a human cell line that is potentially less immunogenic for the treatment of hemophilia A. *Human-cl rhFVIII* is a fourth-generation, BDD rFVIII concentrate, which is produced in genetically modified human embryonic kidney (HEK) 293F cells.

The clinical development of *Human-cl rhFVIII* for this BLA was conducted under IND 13722. During the Pre-BLA meeting on September 12, 2013, the FDA requested the applicant to modify their statistical analysis method for estimating the annualized bleeding rate (ABR). Specifically, the FDA recommended calculating the average individualized ABR and its 95% confidence interval using a generalized linear model with log link for Poisson model. Efficacious routine prophylaxis with the product can be shown by reducing the mean ABR of subjects with prophylactic treatment by at least 50% when compared to the mean ABR of subjects treated on-demand (GENA-08 vs. GENA-01 and GENA-03 vs. GENA-01). The applicant submitted the BLA on June 5, 2014.

On November 11, 2014, an information request was sent to the applicant to clarify the result discrepancy regarding the analysis of overall treatment efficacy in study GENA-01. The applicant responded on December 5, 2014 (amendment STN125555/0.13) with two additional datasets along with SAS programs for the primary efficacy analysis of study GENA-01.

During the review and communication with the applicant, FDA realized the applicant meant using *Human-cl rhFVIII* for routine prophylaxis in addition to the on-demand treatment and control indication. On April 29, 2015, the applicant submitted a revised package insert (PI) indicating that they misunderstood the use of the term “prevent” and thought they had requested an indication for “prophylaxis”. The revised PI specified an indication for “routine prophylaxis”, dosing information, and some prophylaxis analysis results from the clinical studies. In the late-cycle meeting (a teleconference) with applicant on May 4, 2015, FDA clarified that if applicant also seeks an approval for prophylaxis, they need to submit the analysis-ready data sets to support the statistical review for the prophylaxis use. On May 8, 2015, the applicant submitted the major amendment (STN125555/0.43) with the requested datasets and SAS programs to support the prophylaxis indication in the updated eCTD file. The review clock was extended to September 4, 2015 due to this major amendment.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

All data sources are included in the applicant's eCTD submission located in the FDA/CBER Electronic Document Room (EDR) at the following link:

(b) (4)

5.1 Review Strategy

There are six clinical studies in this BLA application. Per discussion within the Pre-BLA meeting, three studies (GENA-01, GENA-08 and GENA-03) are the pivotal studies for this submission. Study GENA-01 recruited mostly adult subjects and two adolescents. GENA-08 was designed to enroll adolescent previously treated subjects (PTPs) in addition to adults (planned ages 12–65 years), but it ended up recruiting only adults (>18 years). GENA-03 was a pediatric study in subjects aged 2 to 12 years. Two studies (GENA-09 and its extension GENA-04) are included as supportive studies, mainly for assessment of inhibitor development and surgical prophylaxis. These two studies were conducted in a single center in Russia and exclusively in adult PTPs. One study (GENA-11) was an extension study of pivotal trial GENA-01, which was initiated to assess the long-term safety and efficacy of on-demand treatment with *Human-cl rhFVIII*. This review memo focuses on the primary efficacy analysis of three pivotal studies.

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

The documents reviewed in the original submission STN 125555/0 include:

- Clinical Overview (module 2.5)
- Summary of Clinical Efficacy (module 2.7.3)
- Summary of Clinical Safety (module 2.7.4)
- Clinical Study Reports and tabulations for Study GENA-01, GENA-08, GENA-03, GENA-09 and GENA-04 (module 5.3.5.2)
- Clinical Study Report Addendums for Study GENA-08 and GENA-03
- Overview of Surgeries in the GENA studies (module 5.3.5.3)

Analyses performed within this review are based on following analysis-ready datasets provided by the applicant.

— STN 125555/0.0

- dm.xpt, vs.xpt, op.xpt and ae.xpt from Study GENA-0
- dm.xpt, vs.xpt, op.xpt, bl.xpt, suppbl.xpt and ae.xpt from Study GENA-08
- dm.xpt, vs.xpt, op.xpt, bl.xpt, suppbl.xpt and ae.xpt from Study GENA-03
- op.xpt from Study GENA-09
- op.xpt from Study GENA-04

- STN 125555/0.13
 - adbleff.xpt from Study GENA-01

- STN 125555/0.43
 - adabr.xpt from Study GENA-08
 - adabr.xpt from Study GENA-03

The reviewer verified all efficacy results against the data provided by the sponsor using version 9.3 of SAS.

5.3 Table of Studies/Clinical Trials

Three pivotal studies (GENA-01, GENA-08 and GENA-03) and two supportive studies (GENA-09 and GENA-04) in this BLA submission are summarized in Table 1. In this memo, three pivotal studies will be reviewed in detail (see Section 6) and two supportive studies will be briefly reviewed in the integrated overview of efficacy which focuses on the surgery prophylaxis indication (see Section 7). Study GENA-11, also included in this submission, only enrolled 3 subjects from one study center and is not reviewed in this memo.

Table 1 Summary of Completed Clinical Studies with *Human-cl rhFVIII*

Study No.	Population/ No. of patients/ Planned age (enrolled age)	Design/ Study Site/ Location/ Study Period	Endpoints
GENA-01	PTPs with ≥ 150 EDs N=22 ≥ 12 and ≤ 65 years (12–65 years)	Prospective, randomized, cross-over, open-label, Phase II Multicenter: 9 centers in Germany, Bulgaria and USA Start: 07-Jun-2010 End: 18-Sep-2012	<u>Primary</u> PK: AUC (FVIII:C) vs Kogenate FS (normalized for administered dose) <u>Secondary</u> PK: $T_{1/2}$, C_{max} , T_{max} , MRT, V_{ss} , CL, and IVR Efficacy: treatment of BEs, surgical prophylaxis Safety: tolerability and immunogenicity
GENA-08	PTPs with ≥ 150 EDs N=32 ≥ 12 years (18–75 years)	Prospective, open-label, Phase III Multicenter 11 centers in Austria, Bulgaria, Germany, UK Start: 22-Jun-2010 End: 31-Jan-2012	<u>Primary</u> Efficacy: prophylaxis, treatment of BEs, surgical prophylaxis <u>Secondary</u> PK: IVR Safety: tolerability and immunogenicity

Table 1. Summary of Completed Clinical Studies with *Human-cl rhFVIII* (Cont.)

Study No.	Population/ No. of patients/ Planned age (enrolled age)	Design/ Study Site/ Location/ Study Period	Endpoints
GENA-03	PTPs with ≥ 50 EDs N=59 ≥ 2 and ≤ 12 years (2–5 years N=29, 6–12 years N=30)	Prospective, non-controlled, open-label, Phase III Multicenter: 15 centers in Czech Republic, Poland, Russia, Turkey, France, Romania and UK Start: 27-Dec-2010 End: 06-Nov-2012	<u>Primary</u> <i>Efficacy</i> : Prevention and treatment of BEs <u>Secondary</u> <i>PK</i> : AUC, IVR, $T_{1/2}$, C_{max} , T_{max} , MRT, V_{ss} and CL versus patients' previous FVIII products <i>Efficacy</i> : surgical prophylaxis <i>Safety</i> : tolerability and immunogenicity
	GENA-09	PTPs with ≥ 150 EDs N=22 ≥ 18 and ≤ 65 years (18–62 years) Single center Russia Start: 16-Mar- 2009 End: 26-May-2010	<u>Primary</u> <i>PK</i> : AUC (FVIII:C) vs Kogenate, (normalized for administered dose) <u>Secondary</u> <i>PK</i> : IVR, $T_{1/2}$, C_{max} , T_{max} , MRT, V_{ss} and CL <i>Efficacy</i> : prophylaxis, treatment of BEs, surgical prophylaxis <i>Safety</i> : tolerability and immunogenicity
GENA-04	PTPs who participated in GENA-09 N=18 ≥ 18 and ≤ 65 years (18–62 years)	Open-label extension of GENA-09 Single center Russia Start: 21-Nov-2009 End: 28-Jul-2011	<u>Primary</u> <i>Safety</i> : Long-term immunogenicity and tolerability <u>Secondary</u> <i>Efficacy</i> : prophylaxis, treatment of BEs, surgical prophylaxis <i>PK</i> : IVR

Source: Original BLA 125555/0; Clinical Overview, p. 9 - 10.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study GENA-01

6.1.1 Objectives (Primary, Secondary, etc.)

The primary objective of this study was to determine the pharmacokinetics (PK) of *Human-cl rhFVIII* in terms of the human coagulation factor VIII coagulant activity

(FVIII:C) and to compare it with the licensed FVIII concentrate Kogenate FS in PTPs suffering from severe hemophilia A.

The secondary objectives of the study were:

- To calculate the incremental recovery of FVIII:C for *Human-cl rhFVIII*
- To investigate the immunogenic potential of *Human-cl rhFVIII*
- To assess clinical efficacy and safety of *Human-cl rhFVIII* in the treatment of BEs
- To assess clinical efficacy and safety of *Human-cl rhFVIII* in surgical prophylaxis

6.1.2 Design Overview

This was a prospective, randomized, actively controlled, open-label, cross-over, multicenter Phase II study. PK of *Human-cl rhFVIII* and Kogenate FS were assessed in Part I of the study. In Part II, subjects who completed Part I were followed up for a period of at least 50 exposure days (EDs) or at least 6 months using *Human-cl rhFVIII*, whichever came last. Visit for PK Cycle 1 was to be scheduled within 4 weeks after the screening visit. Subjects were randomized to treatment sequences consisting of two cycles (*Human-cl rhFVIII* followed by Kogenate FS, or Kogenate FS followed by *Human-cl rhFVIII*) with a randomization ratio of 1:1. All subjects who completed Part I of the study were to continue with on-demand treatment (Part II) with *Human-cl rhFVIII*. The start of Part II was defined as the first day after the last PK sample was taken during PK Cycle 2. The 6-month (+2 weeks) visit consisted of a full PK analysis with *Human-cl rhFVIII* as well as a study completion assessment for subjects who had at least 50 EDs documented under *Human-cl rhFVIII* treatment. Subjects with less than 50 EDs at this point were to have additional visits every 3 months until achievement of 50 EDs. For subjects undergoing surgical interventions, treatment details were documented for the pre-, intra-, and postoperative phase.

6.1.3 Population

Each subject had to satisfy the following criteria before study entry:

1. Must have severe hemophilia A (FVIII:C \leq 1%; historical value as documented in patient records)
2. Male subjects \geq 12 and \leq 65 years of age
3. Body weight (BW) 25 kg to 110 kg
4. Previously treated with FVIII concentrate, at least 150 EDs
5. Immunocompetent (CD4+ count $>$ 200/ μ L)
6. Negative for anti-HIV; if positive, viral load less than 200 particles/ μ L or less than 400,000 copies/mL
7. Freely given written informed consent

Subjects were not included if any of the following exclusion criteria were met:

1. Other coagulation disorder than hemophilia A
2. Present or past FVIII inhibitor activity (\geq 0.6 Bethesda Units [BU])
3. Severe liver or kidney disease (alanine aminotransferase [ALT] and aspartate aminotransferase [AST] levels $>$ 5 times of upper limit of normal, creatinine $>$ 120 μ mol/L)

4. Receiving or scheduled to receive immuno-modulating drugs (other than antiretroviral chemotherapy) such as alpha-interferon, prednisone (equivalent to >10 mg/day), or similar drugs
5. Participation in another interventional clinical study currently or during the past month

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects were randomized to receive 50 international units (IU) FVIII/kg BW (labelled potency) of either *Human-cl rhFVIII* or Kogenate FS in Cycle 1 and the other product in Cycle 2 after a FVIII wash-out period of at least 96 hours. The required dosage for the on-demand treatment period was determined using the following formula:

$$\text{Required units} = \text{BW (kg)} * \text{desired FVIII rise (\%)} (\text{IU/dL}) * 0.5 \\ (\text{assuming that the recovery of FVIII is } 2\% / [\text{IU/kg}])$$

For the subjects undergoing surgical procedures, the required dosage of *Human-cl rhFVIII* was determined using the following formula:

$$\text{Dose} = \text{target increase of FVIII (IU/dL)} * \text{BW/actual in vivo recovery (IVR)} \\ (\text{IU/dL}) / (\text{IU/kg}).$$

The investigational medicinal product (IMP) was to be administered as an intravenous bolus injection.

6.1.6 Sites and Centers

This study was conducted in nine investigational centers in Bulgaria, Germany and the US.

6.1.8 Endpoints and Criteria for Study Success

The efficacy of *Human-cl rhFVIII* was evaluated using only the data from the on-demand treatment period (Part II) in this study. The efficacy endpoint for on-demand treatment was the proportion of BEs with successful treatment (rated as good or excellent in the efficacy assessment at the end of the BE), while efficacy assessment was made by the subject (together with the investigator in case of on-site treatment) as follows:

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

If the lower 95% confidence limit for the rate of successfully treated BEs was >70%, on-demand treatment with *Human-cl rhFVIII* would be claimed effective.

The ABR for each subject was calculated as follows:

$$\text{ABR} = \frac{\text{Number of all types of BEs during the } \geq 6 \text{ month on demand treatment period}}{\text{duration of the "observed on demand treatment period" in days}} \times 365.25$$

For the subjects undergoing surgical interventions, an overall efficacy assessment taking both the intra- and post-operative assessment into account was to be done by the surgeon and the hematologist. Details on the efficacy scales and endpoint are specified in Section 7.1.1.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Analysis Populations

- Safety population (SAF): All subjects who received at least one dose of *Human-cl rhFVIII*. All safety endpoints were analyzed using the SAF.
- Intention-to-Treat (ITT) population: All subjects in the safety analysis population for whom any data was collected post treatment with *Human-cl rhFVIII*. The primary efficacy analysis was planned using the ITT population.
- Per-Protocol (PP) population: All subjects in the ITT population who completed the study without significantly violating the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the efficacy results.

Surgery populations are defined in Section 7.1.1.

Analysis for Efficacy Endpoint

A formal statistical test was to be performed to test whether the proportion is significantly higher than 70%:

$$H_0: p_{\text{success}} \leq 0.7 \text{ vs } H_1: p_{\text{success}} > 0.7$$

where p_{success} represents the overall proportion of successfully treated BEs. A 2-sided 95% Clopper-Pearson CI was built around the estimate of p_{success} .

Sample Size

It was planned to include a total of 20 to 25 subjects in the study based on a cross-over PK study design. Assuming independent binomially distributed success within subjects and centers, the expected 1000 bleeding events in this study can serve to show that the rate of successful treatments (hemostatic efficacy rated good or excellent) is above 70% ($\alpha=0.025$, one-sided) if the true success rate is 75% or better with a power of at least 94%.

Missing Data Handling

If the treatment efficacy evaluation for a BE was missing, the bleeding was considered as treated not successfully in the ITT analysis and was excluded from the PP analysis.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

A total of 22 subjects were enrolled in this study and included in the SAF and ITT populations. Of these, 14 subjects were included in the PP population.

Two subjects underwent two surgical procedures: one major and one minor.

6.1.10.1.1 Demographics

The demographic characteristics of the ITT/SAF populations are shown in Table 2. All subjects were male.

**Table 2. Demographic Characteristics of Study Population
(ITT/SAF Population, N=22)**

Parameter	Mean	SD	Median	Range
Age (years)	39.6	14.06	41.0	12-65
Height (cm)	174.0	9.41	176.0	154-188
Weight (kg)	72.7	15.55	69.5	46-105
BMI (kg/m ²)	23.9	4.79	23.0	19-36
Parameter			N	Percentage
Race	American Indian or Alaska Native		1	4.5
	White		18	81.8
	Black or African American		3	13.6

Source: Original BLA 125555/0; Clinical Study Report for Study GENA-01, p. 59.

6.1.10.1.3 Subject Disposition

A total of 24 subjects were screened and 22 were randomized in Part I, PK study. Of these, 21 completed the Part I and Part II of the study. No subjects discontinued the study due to an AE. One subject terminated the study prematurely due to loss to follow-up.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Efficacy Endpoint

A total of 986 BEs were documented in subjects in the ITT population (N=22) for which any amount of treatment with *Human-cl rhFVIII* was documented and started between initiation of home treatment after PK Cycle 2 (i.e., one day after drawing of last blood sample for PK) and the completion visit. Of the 986 BEs, 642 (65.1%) were spontaneous, 341 (34.6%) were traumatic, and 3 (0.3%) were due to other causes.

Efficacy assessments were available for 985 BEs and missing for 1 BE. Overall, 94.4% (931/986) of the BEs were treated with excellent or good efficacy outcomes (60.3% excellent, 34.1% good). Treatment efficacy was judged as moderate in 5.5% of BEs. No BE was *Human-cl rhFVIII* treatment judged as having no efficacy. The proportion of BEs with successful treatment was 94.4%, with a 95% confidence interval (CI) of 92.8%, 95.8%. Thus, as the lower confidence limit for the rate of successfully treated BEs was >70%, on-demand treatment with *Human-cl rhFVIII* is claimed effective. A similar direction is revealed in the PP analysis (N=14), that is, the success rate for the subjects treated per-protocol was 97.6% (653/669 BEs) with a 95% confidence limit of 96.1%, 98.6%.

The mean ABRs were 58.08 (SD 30.78; median 54.49; range 9.35-129.81) with a 95% CI of 44.43, 71.73 for all types of bleeds and 38.46 (SD 28.07; median 40.55; range 0–99.27) with a 95% CI of 26.01, 50.90 for spontaneous bleeds.

Two subjects underwent two surgical procedures. No maintenance infusions were needed during surgery. Both intra-operative and overall efficacy of *Human-cl rhFVIII* was rated as excellent for both surgeries (see Section 7.1.1).

6.1.11.3 Subpopulation Analyses

No subgroup analysis was planned by the applicant. This reviewer performed subgroup analyses for the efficacy endpoint by race, country and age categories using the ITT population (Table 3). There are no efficacy concerns with these subgroups.

Table 3. The proportion of BEs with successful treatment by subgroup (ITT population)

Subgroup	Proportion of BEs with successful treatment (%)
Race	
American Indian Or Alaska Native (N=1)	93/93 (100%)
Black or African American (N=3)	131/131 (100%)
White (N=18)	707/762 (92.8%)
Age	
<16 years (N=2)	94/97 (96.9%)
>=16 years (N=20)	837/889 (94.2%)
Country	
USA (N=10)	392/429 (91.38%)
Non-USA (N=12)	539/557 (96.77%)

6.1.11.4 Dropouts and/or Discontinuations

Please refer to section 6.1.10.1.3.

6.1.12 Safety Analyses

A total of 12 (54.5%) subjects experienced 69 treatment-emergent AEs. Three serious adverse events (SAEs) occurred in two subjects. All AEs/SAEs were deemed unrelated to study treatment. No death occurred during this study. No cases of thromboembolism were observed. No FVIII inhibitors were detected. The safety analysis is summarized in Table 4. Note that a SAE was any untoward medical occurrence that at any dose results in death, life-threatening, hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other important medical event. The severity of AEs was categorized as follows:

- Mild: experience that was minor and did not cause significant discomfort to subject or change in routine activities;
- Moderate: limitation in activity – some assistance may be needed; no or minimal medical intervention/therapy required.
- Severe: marked limitation in activity – some assistance required; medical intervention/therapy required.

Table 4. Summary Statistics on AEs

Category	Patients with at least one AE occurrence (SAF population, N=22)	
	n	%
AE	12	54.5
Probably or possibly related AE	0	0.0
SAE	2	9.1
Probably or possibly related SAE	0	0.0
Severe AE	3	13.6
Temporally related AE*	8	36.4
Death	0	0.0
Death due to probably or possibly related AE	0	0.0
AE leading to discontinuation of study product	0	0.0
Probably or possibly related AE leading to discontinuation of study product	0	0.0

Source: Original BLA 125555/0; Clinical Study Report for Study GENA-01, p. 84.

6.2 Study GENA-08

6.2.1 Objectives (Primary, Secondary, etc.)

The primary objective of this study was to determine in PTPs with severe hemophilia A the efficacy of *Human-cl rhFVIII* during prophylactic treatment, in the treatment of BEs and in surgical prophylaxis.

The secondary objectives of the study were:

- To calculate the incremental recovery of FVIII:C activity for *Human-cl rhFVIII*
- To investigate the immunogenic potential of *Human-cl rhFVIII*
- To assess the safety of *Human-cl rhFVIII*

6.2.2 Design Overview

This was a prospective, open-label, international, non-controlled, multicenter Phase 3 study. After the screening visit and IVR assessment at Visit 1, the subjects entered the open treatment phase where they were treated prophylactically (including surgery prophylaxis, if any) and on-demand (in case of breakthrough bleeds) for a period of 6 months and at least 50 EDs. Follow-up visits were scheduled after 10–15 EDs and at 3 months (± 2 weeks) and 6 months ($+2$ weeks).

The dosage and frequency of *Human-cl rhFVIII* treatment during the study was determined by the individual patient's clinical situation. Subjects were to receive *Human-cl rhFVIII* prophylactically every other day and, if required, for treatment of breakthrough BEs or in case of surgical interventions, for the entire duration of the study.

6.2.3 Population

Each subject had to satisfy the following criteria before study entry:

1. Must have severe hemophilia A (FVIII:C $\leq 1\%$; historical value as documented in patient records)
2. Male subjects 12 years of age or older
3. Previously treated with FVIII concentrate, at least 150 EDs
4. Immunocompetent (CD4+ count $>200/\mu\text{L}$)
5. Negative for anti-human immunodeficiency virus; if positive, viral load less than 200 particles/ μL or less than 400,000 copies/mL
6. Freely given written informed consent

Subjects were not included if any of the following exclusion criteria were met:

1. Other coagulation disorder than hemophilia A
2. Present or past FVIII inhibitor activity (≥ 0.6 BU)
3. Severe liver or kidney disease (ALT and AST >5 times of upper limit of normal, creatinine >120 $\mu\text{mol/L}$)
4. Receiving or scheduled to receive immuno-modulating drugs (other than antiretroviral chemotherapy) such as alpha-interferon, prednisone (equivalent to >10 mg/day), or similar drugs
5. Participation in another interventional clinical study currently or during the past month
6. Participation in any other study with *Human-cl rhFVIII*

6.2.4 Study Treatments or Agents Mandated by the Protocol

Human-cl rhFVIII was administered to all subjects prophylactically, for treatment of BEs or in case of surgical procedures. Subjects being treated prophylactically were to receive 30–40 IU FVIII/kg every other day until 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).

The dosage (and duration) of treatment of spontaneous or traumatic breakthrough BEs during the prophylactic treatment period depended on the location and extent of bleeding and on the clinical situation of the subject. The required dosage was determined using the following formula:

$$\text{Required units} = \text{BW (kg)} * \text{desired FVIII rise (\%)} (\text{IU/dL}) * 0.5$$

(assuming that the recovery of FVIII is 2%/(IU/kg))

For subjects undergoing surgical interventions, the required prophylactic dosage was determined using the following formula:

$$\text{Dose} = \text{target increase of FVIII (IU/dL)} * \text{BW(kg)/actual IVR (IU/dL)/(IU/kg)}$$

6.2.6 Sites and Centers

This study was conducted in 11 investigational centers in Austria, Bulgaria, Germany and the UK.

6.2.8 Endpoints and Criteria for Study Success

The primary efficacy endpoint was ABR, which was calculated for each subject as follows:

$$\text{ABR} = \frac{\text{Number of all types of BEs during the } \geq 6 \text{ month prophylactic treatment period}}{\text{duration of the "observed prophylactic treatment period" in days}} \times 365.25$$

Secondary efficacy endpoints include:

- 1) The number of BEs that occurred during the prophylactic treatment period;
- 2) The monthly bleeding rate for all types of bleedings;
- 3) Assessment for treating break-through bleedings using the following four-point scale:
 - *Excellent*: Abrupt pain relief and/or unequivocal improvement in objective signs of bleeding within approximately 8 hours after a single infusion
 - *Good*: Definite pain relief and/or improvement in signs of bleeding within approximately 8–12 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

For the subjects undergoing surgical interventions, an overall efficacy assessment taking both the intra- and post-operative assessment into account was to be done by the surgeon and the hematologist. Details on the efficacy scales and endpoint are specified in Section 7.1.1.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Analysis Populations

Three basic populations were considered:

- SAF set: All subjects who received at least one dose of *Human-cl rhFVIII*.
- ITT set: All subjects in the safety analysis population for whom any data was collected post treatment with *Human-cl rhFVIII*. The ITT population was considered to be the primary analyses set for efficacy data.
- PP set: All subjects in the ITT analysis population who completed the study without significantly violating the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the efficacy results.

Surgery populations are defined in Section 7.1.1.

Analysis for Primary Efficacy Endpoint

No confirmative statistical analysis was planned within Study GENA-08. In order to demonstrating the efficacy of the prophylactic treatment, the following test of hypothesis was added to the application later on and agreed to by FDA.

A test on the rate ratio of mean ABRs with hypotheses

$$H_0: RR_{c/p} = \lambda_{\text{year,control}} / \lambda_{\text{year,proph}} \leq 2$$
$$H_a: RR_{c/p} = \lambda_{\text{year,control}} / \lambda_{\text{year,proph}} > 2$$

was to be performed using a Poisson regression model or a negative binomial regression model corrected for over dispersion, where $\lambda_{\text{year,proph}}$ represents the mean ABR of prophylactically treated subjects (GENA-08) through a projected one-year period of prophylactic treatment; $\lambda_{\text{year,control}}$ represents the respective mean ABR for all on demand treated subjects (GENA-01).

The H_0 hypothesis was to be rejected if the lower limit of the two-sided 95% CI for $RR_{c/p}$ is > 2 , which was equivalent to the upper limit of the two-sided 95% CI for $1/RR_{c/p} < 0.5$.

Sample Size

It was planned to include a total of 32 evaluable subjects into the study. No formal sample size estimation was performed.

Missing Data Handling

There was no plan for handling missing data of efficacy endpoints provided.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

A total of 32 subjects were enrolled in this study and included in the safety (SAF) and the ITT population. Of the 32 subjects, 26 subjects were included in the PP population.

6.2.10.1.1 Demographics

Table 5 summarizes the demographics for the ITT/SAF population reported by the applicant. All subjects enrolled were male.

**Table 5. Demographic Characteristics of Study Population
(ITT/SAF Population, N=32)**

Parameter	Mean	SD	Median	Range
Age at first treatment (years)*	37.3	13.6	35.0	18–75
Height (cm)	178.4	7.9	180.0	158–192
Weight (kg)	82.5	18.0	84.5	47–127
Parameter			N	Percentage
Race	Asian		3	9.4
	White		29	90.6

Source: Original BLA 125555/0; Clinical Study Report for Study GENA-08, P. 46.

6.2.10.1.3 Subject Disposition

Of the 32 subjects enrolled this study, 30 subjects completed the study according to the protocol. Two subjects terminated the study prematurely: one withdrew his consent after 17 EDs and another died on Day 202.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

The mean ABRs were 2.28 (SD 3.73; median 0.9; range 0–14.69) with a 95% CI of 0.94, 3.63 for all types of bleeds and 1.16 (SD 2.57; median 0; range 0–8.6) with a 95% CI of 0.24, 2.09 for spontaneous bleeds.

A negative binomial regression model corrected for over dispersion showed that the ratio of the mean ABRs of GENA-08 vs. GENA-01 was 0.04 with a 95% CI of 0.02, 0.07, which is equivalent to a 96% reduction in mean ABR in prophylactic treatment compared to on-demand treatment. The upper bound of the 95% CI for the ratio was less than 0.5 and therefore the successful criterion for prophylaxis efficacy was met.

A total of 44 BEs occurred during the study at any time after the start of study treatment within the ITT population. Of the 44 BEs, 28 (63.6%) were minor bleeds and 16 (36.4%)

were moderate to major bleeds. Twenty-six bleeds (59.1%) were spontaneous, 16 (36.4%) were traumatic bleeds, and 2 bleeds (4.5%) were due to other causes.

Out of 32 subjects in the ITT population, 16 (50%) did not experience any BEs and 11 (34.4%) experienced only one BE, and 5 subjects had 5 or more BEs during the study. The mean monthly bleeding rates during the prophylactic treatment period at the end of the study were 0.095 for spontaneous bleeds (SD 0.211; median 0; range 0–0.71) and 0.188 (SD 0.307; median 0.074; range 0–1.21) for all types of bleeds.

Out of the 44 BEs that occurred during the study, 30 BEs occurred in 15 subjects and were treated with at least one dose of *Human-cl rhFVIII*, and 14 BEs occurred in 4 subjects and were not treated. Of the 30 BEs, efficacy assessments of *Human-cl rhFVIII* for treating breakthrough bleedings were available for 28 BEs: 20 (71.4%) were rated as “excellent” and 8 (28.6%) were rated as “Good”.

During this study, six patients underwent six surgical procedures, five of which were major surgeries. No maintenance doses during surgery were required in any subject. For four surgeries (the minor and three major procedures), the overall efficacy was rated as excellent, while the overall efficacy was rated as moderate for one major surgery. See Section 7.1.1 for analysis of the surgery endpoint.

6.2.11.4 Dropouts and/or Discontinuations

Please refer to section 6.2.10.1.3.

6.2.12 Safety Analyses

A total of 65 treatment-emergent AEs were recorded in 21 of the 32 subjects (65.6%). One death occurred during the study due to an epileptic seizure that was deemed unrelated to study treatment. Two SAEs occurred in two subjects and were deemed unrelated to study treatment. No cases of thromboembolism were observed. No FVIII inhibitors or anti-FVIII antibodies were detected

Table 6 shows the summary of safety analysis in the safety population. See Section 6.1.12 for definitions of SAE and the severity of AEs.

Table 6. Summary Statistics on AEs (SAF Population, N=32)

Category	Patients with at least one occurrence	
	n	%
AE	21	65.6
Probably or possibly related AE	2	6.3
SAE	2	6.3
Probably or possibly related SAE	0	0.0
Severe AE	4	12.5
Temporally related AE*	15	46.9
Death	1	3.1
Death due to probably or possibly related AE	0	0.0
AE leading to discontinuation of study product [†]	1	3.1
Probably or possibly related AE leading to discontinuation of study product [‡]	0	0.0
SAE or AE leading to discontinuation of study product [†]	2	6.3

Source: Original BLA 125555/0; Clinical Study Report for Study GENA-08, p. 63.

6.3 Study GENA-03

6.3.1 Objectives (Primary, Secondary, etc)

Primary Objective

The primary objective of this clinical study was to assess clinical efficacy of *Human-cl rhFVIII* in terms of prevention (prophylactic treatment) and treatment of (breakthrough) BEs in previously treated children suffering from severe hemophilia A (FVIII:C <1%).

Secondary Objectives

- To determine PK of *Human-cl rhFVIII*
- To determine the incremental recovery of *Human-cl rhFVIII* – also over time;
- To investigate the immunogenic potential of *Human-cl rhFVIII* by assessing the inhibitor titer;
- To assess efficacy of *Human-cl rhFVIII* in surgeries;
- To assess safety of *Human-cl rhFVIII* in terms of AE monitoring.

6.3.2 Design Overview

This study was designed as a prospective, non-controlled, open label, multinational, multicenter Phase 3 study in pediatric subjects with severe hemophilia A (FVIII:C <1%) and who were allocated to one of two age cohorts (30 PTPs aged 2–5 years, and 30 PTPs aged 6–12 years), all exhibiting at least 50 previous EDs to FVIII concentrates. After the screening visit, subjects with consent participated in the PK phase (Phase I) of the study. Subjects who completed Phase I and further enrolled subjects were followed up for a

period of at least 6 months and at least 50 EDs (Phase II). During this phase, prophylactic and on-demand treatments (in case of breakthrough bleeds) with *Human-cl rhFVIII* were documented. 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). The overall efficacy assessment of prophylactic treatment was performed per subject after 50 EDs and at the end of the study. In subjects who underwent surgical interventions, treatment details were documented for the pre-, intra-, and postoperative phase, respectively.

6.3.3 Population

Each subject had to satisfy the following criteria before study entry:

1. Severe hemophilia A (FVIII:C $<1\%$);
2. Age ≥ 2 and ≤ 12 years;
3. Previously treated with FVIII concentrate, at least 50 EDs;
4. Immunocompetence (CD4+ count $>200/\mu\text{L}$);
5. Human immunodeficiency virus (HIV)-negative or respective viral load <200 particles/ μL or $<400,000$ copies/mL;
6. Freely given written informed consent by parents or legal guardian and by subjects (depending on their developmental stage and intellectual capacity).

Subjects were not included if any of the following exclusion criteria were met:

1. Other coagulation disorder than hemophilia A;
2. Present or past FVIII inhibitor activity (≥ 0.6 BU);
3. Target joints;
4. Severe liver or kidney disease (ALT and AST levels >5 times of upper limit of normal, creatinine >120 $\mu\text{mol/L}$);
5. Receipt or scheduled receipt of immuno-modulating drugs (other than antiretroviral chemotherapy) such as alpha-interferon, prednisone (>10 mg/day), or comparable drugs;
6. Current participation in another clinical study;
7. Participation in another interventional clinical study with administration of IMP in the course of the past 3 months, except studies investigating already registered FVIII products.

6.3.4 Study Treatments or Agents Mandated by the Protocol

Human-cl rhFVIII was administered at a dose of 50 IU/kg BW for PK and IVR assessments in Phases I and II. For prophylactic treatment in Phase II, 30–40 IU FVIII/kg BW of *Human-cl rhFVIII* were administered every other day or 3 times weekly until 6 months and ≥ 50 EDs had been fulfilled. Two dose escalations of each $+5$ IU/kg BW were allowed in case of an inadequate response (≥ 2 spontaneous BEs within one month). The dosage and duration of treating spontaneous or traumatic breakthrough BEs within the prophylactic treatment period depended both on the location and on the extent of bleeding, and on the clinical condition of the respective subject. The required dosage was determined using the following formula:

$$\text{Required units} = \text{BW (kg)} * \text{desired FVIII rise (\%)} * 0.5$$

(assuming the recovery of FVIII to be 2 %/[IU/kg]).

For subjects undergoing surgeries, the required prophylaxis dosage was determined using the following formula:

$$\text{Dose} = \text{target increase of FVIII (IU/dL)} * \text{BW(kg)/actual IVR (IU/dL)/(IU/kg)}.$$

6.3.6 Sites and Centers

This study was conducted at 15 investigational centers in the UK, Czech Republic, Poland, Russia, Turkey, France and Romania.

6.3.8 Endpoints and Criteria for Study Success

The primary efficacy endpoint was annualized bleeding rate (ABR), which was calculated for each subject as follows:

$$\text{ABR} = \frac{\text{Number of all types of BEs during the } \geq 6 \text{ month prophylactic treatment period}}{\text{duration of the "observed prophylactic treatment period" in days}} \times 365.25$$

Secondary efficacy endpoints include:

- 1) The number of BEs that occurred during the prophylactic treatment period;
- 2) The monthly bleeding rate for all types of bleedings;
- 3) Assessment for treating break-through bleedings using the following four-point scale:
 - *Excellent*: Abrupt pain relief and/or unequivocal improvement in objective signs of bleeding within approximately 8 hours after a single infusion
 - *Good*: Definite pain relief and/or improvement in signs of bleeding within approximately 8–12 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

For the subjects undergoing surgical interventions, an overall efficacy assessment taking both the intra- and post-operative assessment into account was to be done by the surgeon and the hematologist. Details on the efficacy scales and endpoint are specified in Section 7.1.1.

6.3.9 Statistical Considerations & Statistical Analysis Plan

Analysis Populations

- Safety Set (SAFETY): All subjects who received at least one dose of *Human-cl rhFVIII*.

- ITT Set: All subjects in the safety set for whom any data was collected post treatment with *Human-cl rhFVIII*. The ITT population was the primary analyses set for efficacy endpoint.
- PP Set: All subjects in the ITT analysis population who completed the trial without significantly violating the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the efficacy results.

Surgery populations are defined in Section 7.1.1.

Analysis of Efficacy Endpoints

No inferential analysis involving formal testing was planned within Study GENA-03. In order to demonstrating the efficacy of the prophylactic treatment, the following test of hypothesis was added to the application later on and agreed to by FDA.

A test on the rate ratio of mean ABRs with hypotheses

$$H_0: RR_{c/p} = \lambda_{\text{year,control}} / \lambda_{\text{year,proph}} \leq 2$$

$$H_a: RR_{c/p} = \lambda_{\text{year,control}} / \lambda_{\text{year,proph}} > 2$$

was to be performed using a Poisson regression model or a negative binomial regression model corrected for over dispersion, where $\lambda_{\text{year,proph}}$ represents the mean ABR of prophylactically treated subjects (GENA-03) through a projected one-year period of prophylactic treatment; $\lambda_{\text{year,control}}$ represents the respective mean ABR for all on demand treated subjects (GENA-01).

The H_0 hypothesis was to be rejected if the lower limit of the two-sided 95% CI for $RR_{c/p}$ is > 2 , which was equivalent to the upper limit of the two-sided 95% CI for $1/RR_{c/p} < 0.5$.

Sample Size

No formal sample size estimation was performed. A total of 60 subjects (30 aged 2–5 years and 30 aged 6–12 years) were planned according to the CHMP Guideline on the Clinical Investigation of new FVIII products. The investigation of the PK properties of *Human-cl rhFVIII* and the previously used FVIII concentrate in up to 13 subjects (12 evaluable) of each age cohort was part of the study.

Missing Data Handling

There was no plan for handling missing data of efficacy endpoints.

6.3.10 Study Population and Disposition

6.3.10.1 Populations Enrolled/Analyzed

A total of 59 subjects were enrolled in this study. All 59 subjects were included in the SAFETY and the ITT populations.

6.3.10.1.1 Demographics

All subjects enrolled were white male. Of 59 subjects, 29 subjects were 2 to 5 years old and 30 subjects were 6 to 12 years old. Other demographic characteristics of the ITT population are shown in Table 7.

Table 7. Demographic and Clinical Characteristics of Study Population (ITT/SAFETY Population, N=59)

Parameter	Mean	SD	Median	Range
Age at first study treatment (years)	6.1	2.97	6.0	2–12
Height (cm)	122.5	19.78	122.0	82–173
Weight (kg)	26.7	12.33	22.6	8–73

Source: Original BLA 125555/0; Clinical Study Report for Study GENA-03, p. 64.

6.3.10.1.3 Subject Disposition

Of 59 enrolled subjects in this study, 56 subjects completed the study and 3 subjects prematurely discontinued. One subject was withdrawn from the study due to therapy failure. The other two subjects were withdrawn because of protocol violations.

6.3.11 Efficacy Analyses

6.3.11.1 Analyses of Primary Endpoint(s)

The mean ABRs were 4.12 (SD 5.22; median 1.90; range 0–20.67) with a 95% CI of 2.76, 5.48 for all types of bleeds and 1.50 (SD 3.22; median 0; range 0–13.78) with a 95% CI of 0.63, 2.36 for spontaneous bleeds.

A negative binomial regression model corrected for over dispersion showed that the ratio of the mean ABRs of GENA-03 vs. GENA-01 was 0.07 with a 95% CI of 0.04, 0.11, which is equivalent to a 93% reduction in mean ABR in prophylactic treatment compared to on-demand treatment. The upper bound of the 95% CI for the ratio was less than 0.5 and therefore the successful criterion for prophylaxis efficacy was met.

A total of 129 BEs were experienced by 39 subjects and 20 subjects did not experience any BEs during the prophylactic treatment. Of the 129 BEs, 74 (57.4%) were traumatic, 45 (34.9%) were spontaneous and 10 (7.7%) were due to other causes. One hundred and eight BEs occurred in 32 subjects and were treated with *Human-cl rhFVIII* during the study. Efficacy assessments were available for all 108 BEs. Efficacy ratings were excellent or good for 89 BEs (82.4%; excellent 71.3%, good 11.1%), moderate in 17 (15.7%) BEs and no efficacy in 2 (1.9%) BEs.

The mean monthly bleeding rate was 0.123 BEs/month (SD 0.272; median 0; range 0–1.13) for spontaneous bleeds and 0.338 BEs/month (SD 0.429; median 0.156; range 0–1.70) for all types of bleeds at the end of the study. The monthly rate of traumatic BEs

was lower in subjects age 2 to 5 than in those aged 6 to 12 years (0.113 vs 0.268 BEs/month).

Six subjects underwent six planned surgical procedures under *Human-cl rhFVIII* treatment and all surgeries were major procedures. No maintenance doses during surgery were required for any subject. Efficacy of *Human-cl rhFVIII* was rated as excellent by both the surgeon and the hematologist for five of these surgeries. One subject was later diagnosed with von Willebrand disease (VWD) and withdrawn from the study. Efficacy was not assessed in this subject. See Section 7.1.1. for analysis of the surgery endpoint.

6.3.11.4 Dropouts and/or Discontinuations

Please refer to section 6.3.10.1.3.

6.3.12 Safety Analyses

A total of 124 treatment-emergent AEs were recorded in 38 of the 59 subjects (64.4%). Seven SAEs occurred in five subjects; all seven SAEs were deemed unrelated to study treatment. No deaths occurred during the study. No cases of thromboembolism were observed and no FVIII inhibitors were detected. Table 8 summarizes the safety analysis. See Section 6.1.12 for definitions of SAE and the severity of AEs.

Table 8. Summary Statistics on AEs (SAFETY Set, N=59)

Category	Patients with at least one occurrence	
	N	%
AE	38	64.4
Probably or possibly related AE	2	3.4
SAE	5	8.5
Probably or possibly related SAE	0	0
Severe AE	0	0
Temporally related AE*	33	55.9
Death	0	0
Death due to probably or possibly related AE	0	0
AE leading to discontinuation of study drug	0	0
Probably or possibly related AE leading to discontinuation of study drug	0	0
SAE or AE leading to discontinuation of study drug	5	8.5

Source: Original BLA 125555/0; Clinical Study Report for Study GENA-03, p.102.

7. INTEGRATED OVERVIEW OF EFFICACY

The integrated analysis focused on evaluating efficacy of *Human-cl rhFVIII* in surgical prophylaxis across five studies due to the limited number subjects in each study. As

mentioned in Section 5.3, the five studies include three pivotal studies (GENA-01, GENA-08 and GENA-03) and two supportive studies (GENA-09 and GENA-04).

7.1 Perioperative Management

7.1.1 Methods of Integration

Study designs of the five trials were summarized in Table 1. Subjects who enrolled in any of the five studies and underwent surgical interventions during the studies were included in the integrated analyses.

Study Populations

- Surgery population (SURG): All documented surgical interventions of subjects in the ITT population for which any amount of *Human-cl rhFVIII* prior to, during or after the surgery was documented and no other FVIII concentrate was documented within 24 hours prior to surgery
- Surgery per-protocol population (SURG-PP): All documented surgical interventions of subjects in the PP population for which any amount of *Human-cl rhFVIII* prior to, during or after the surgery was documented and no other FVIII concentrate was documented within 72 hours prior to, during or after the surgery

Primary Efficacy Endpoint

The primary efficacy endpoint was the proportion of successful surgical prophylaxis with *Human-cl rhFVIII*. Successful surgical prophylaxis is defined by the overall efficacy rating of “Excellent” or “Good”, taking both the intra and post-operative assessment into account. The surgeon and hematologist used the following criteria for their assessments. These criteria were used for all five studies.

Intra-operative efficacy (surgeon assessment)

- *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 haemostasis, but hemostasis was controlled.
- *None*: Hemostasis was uncontrolled necessitating a change in clotting factor replacement regimen.

Post-operative efficacy (surgeon and hematologist assessment):

- *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 *Human-cl rhFVIII* 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 *Human-cl rhFVIII* 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.

Statistical Hypothesis:

$$H_0: p \leq 0.7, H_1 p > 0.7$$

where p represents the rate of successful surgical prophylaxis over all surgeries in SURG or SURG-PP. The rate of surgeries with successful prophylaxis is assumed to be binomially distributed with parameter p for each of the populations. One sample binomial tests were performed with one-sided type I error rate of 0.025.

7.1.4 Analysis of Primary Endpoint(s)

Table 9 summarizes the number of surgeries by study. Across all five studies, a total of 34 surgeries occurred in 20 subjects, where 13 procedures in 12 subjects were categorized as major surgeries and 20 procedures in 7 subjects were considered minor surgeries.

Table 9. Number of surgeries in all GENA studies

Study	SURG		SURG-PP	
	# Surgeries	# Subjects with surgeries/ # Subjects in population	# Surgeries	# Subjects with surgeries/ # Subjects in population
GENA-01	2	2/22	1	1/14
GENA-03	6*	6/59	5	5/55
GENA-04	7	3/18	7	3/16
GENA-08	5	5/32	3	3/26
GENA-09	14	4/22	14	4/13
Overall	34	20/153	30	16/124

*Note: one subject was later diagnosed with VWD and withdrawn from the study.

For all surgeries, the intra- and post-operative assessments were identical. Overall 94.1% (32/34) of surgical prophylaxis were rated “Excellent” or “Good” (85.3% excellent; 8.8% good). One (2.9%) surgery was judged as moderate and one surgery was categorized as no efficacy. All 20 minor surgeries and 12 major surgeries were judged as excellent. One

major surgery was rated as moderate. A one sample binomial test showed the overall rate of successful surgical prophylaxis, 94.1%, has a 95% CI of 80.3%, 99.3%. This positive result provides evidence of surgical prophylaxis with *Human-cl rhFVIII*.

The subject’s surgery that was rated as no effect was later diagnosed to have an unrelated disease, rather than Hemophilia A. A sensitivity analysis excluding this subject was also conducted by the applicant. The result in Table 10 shows a similar direction as the results with all surgery data.

Table 10. Analysis of surgical prophylaxis with exclusion of one subject who had misdiagnosed Hemophilia A

Number of surgeries with rating	Major surgeries	Minor surgeries	Total
N	13	20	33
Excellent	9	20	29
Good	3	0	3
Moderate	1	0	1
None	0	0	0
Successful (Excellent or Good)	12/13 (92.3 %)	20/20 (100 %)	32/33 (97.0 %)
95% confidence interval for rating “successful”	64.0 to 99.8 %	83.2 to 100 %	84.2 to >99.9 %
P value for one-sided hypothesis : H0: percentage ≥ 70%	0.064 (Power under H1: Percentage = 92.3%: 35%)	0.0008	0.0002

Source: Original BLA 125555/0; Clinical Study Report for Surgeries in all GENA studies, p. 9.

7.1.11 Efficacy Conclusions

Though the statistical test on the primary efficacy endpoint of successful surgical prophylaxis is exploratory in nature, the results do show some evidence of efficacy of *Human-cl rhFVIII* in surgical prophylaxis.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Six clinical studies were submitted to this BLA, in which three studies (GENA-01, GENA-08 and GENA-03) are considered pivotal studies according to the applicant. Study GENA-01 was a prospective, randomized, actively controlled, open-label cross-over, multicenter Phase 2 study. The active control was utilized for the purpose of evaluating PK (Part I) of *Human-cl rhFVIII*, while the efficacy of on-demand treatment with *Human-cl rhFVIII* was assessed using a formal statistical test on the proportion of BEs with successful treatment (rated as “good” or “excellent”; efficacy assessment at end of BE). The result showed that the proportion of BEs with successful treatment was 94.4% (931/986 BEs) with a 95% CI of 92.8%, 95.8% within the ITT population. As the

lower confidence limit for the rate of successfully treated BEs was >70%, on-demand treatment with *Human-cl rhFVIII* is claimed effective

Of the three pivotal trials, however, two studies (GENA-08 and GENA-03) were non-controlled, single-arm trials conducted outside of the US and with no formal statistical hypothesis planned within the studies. All subjects enrolled in GENA-08 were adults (>18 years old) and GENA-03 was a pediatric study with subjects 2-12 years old. Both studies were considered to assess the efficacy of *Human-cl rhFVIII* in prophylactic treatment. The analyses using negative binomial regression models showed a 96% and 93% reduction in mean ABRs for prophylactic treatment in GENA-08 and GENA-03 compared to on-demand treatment in GENA-01, respectively. As the upper bounds of the 95% CI for the ratio of mean ABRs (GENA-08 vs. GENA-01 and GENA-03 vs. GENA-01) were less than 0.5, these results support prophylaxis efficacy claim for *Human-cl rhFVIII*.

Surgical prophylaxis was assessed via integrated analysis using all documented surgical interventions of subjects in the ITT populations from five studies. The one sample binomial test showed the overall rate of successful surgical prophylaxis, 94.1%, has a 95% CI of 80.3%, 99.3%. The result is considered positive as the lower confidence limit for the rate of successfully treated BEs was >70%, which provides evidence of surgical prophylaxis with *Human-cl rhFVIII*.

No cases of thromboembolism were observed and no FVIII inhibitors were detected for all three pivotal studies. No death occurred in Study GENA-01 and Study GENA-03. One death occurred during Study GENA-08 and was deemed unrelated to study treatment. All SAEs in three studies were deemed unrelated to *Human-cl rhFVIII*.

10.2 Conclusions and Recommendations

In summary, the result of Study GENA-01 showed statistical evidence to support an on-demand use of *Human-cl rhFVIII* in subjects with Hemophilia A. Compared against the on-demand data in Study GENA-01, the routine prophylactic treatment of *Human-cl rhFVIII* was supported by Study GENA-08 and Study GENA-03 for both adult and children subjects with Hemophilia A. Surgical prophylaxis with *Human-cl rhFVIII* was demonstrated via integrated analysis of pooled surgical interventions of subjects from all five GENA studies.

There are no statistical concerns regarding efficacy and safety evaluation in this BLA.