

CLINICAL PHARMACOLOGY BLA REVIEW

Division of Hematology
Office of Blood Review & Research

BLA 125555/0

Product: Nuwiq®, antihemophilic factor (recombinant) plasma/albumin free
Sponsor: Octapharma AG
Indication: Control and prevention of bleeding episodes (also during and after surgery) in adults and children with hemophilia A.
Date Received: June 5, 2014
Reviewer: Carl-Michael Staschen, M.D., Ph.D.
RPM: Jiahua Qian
Through: Iftekhar Mahmood, Ph.D. and Anne Pilaro, Ph.D.

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1. Study Title: 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 Hemophilia A.

Study report GENA-01.

2. Study Title: Prospective clinical study in children with severe Hemophilia A to investigate clinical efficacy, immunogenicity, pharmacokinetics, and safety of *Human-cl rhFVIII*.

Study report GENA-03.

3. Study Title: Clinical study to investigate the pharmacokinetics, efficacy, safety and immunogenicity of *Human-cl rhFVIII* in previously treated patients with severe Hemophilia A.

Study report GENA-09.

4. Study Title: Clinical study to investigate the long-term safety and efficacy of *Human-cl rhFVIII* in previously treated patients with severe Hemophilia A.

Study report GENA-04.

5. Study Title: Clinical study to investigate the efficacy, safety, and immunogenicity of *Human-cl rhFVIII* in previously treated patients with severe Hemophilia A.

Study report GENA-08.

EXECUTIVE SUMMARY

Hemophilia A is an inherited sex-linked disorder of blood coagulation in which affected males do not produce functional coagulation FVIII in sufficient quantities to achieve satisfactory hemostasis. Disease severity is classified according to the level of FVIII activity (% of normal) as mild (>5% to <40%), moderate (1% to 5%) or severe (<1%). Due to deficiencies in FVIII, patients with hemophilia A are predisposed to recurrent bleeding episodes (BEs). The optimal effective treatment of the disorder is replacement of FVIII using FVIII concentrate either obtained by fractionation of human plasma or manufactured by recombinant DNA technology.

Octapharma is developing a recombinant human coagulation factor VIII (Nuwiq®) for the treatment of hemophilia A. Human cell line rhFVIII (*Human-cl rhFVIII*) is a B-domain-deleted rFVIII expressed in genetically modified human embryonic kidney cells. The deleted B-domain has been replaced by a short amino acid linker.

The harvested product is concentrated and purified by a series of chromatography steps. The manufacturing process also includes solvent/detergent (S/D) treatment and nanofiltration steps for virus inactivation/removal. *Human-cl rhFVIII* drug product consists of a white sterile lyophilized powder and a solvent to prepare a solution for injection. The lyophilized powder is supplied in vials containing 250 IU, 500 IU, 1000 IU or 2000 IU rhFVIII per vial, to be reconstituted with 2.5 mL of water for injection.

The applicant is seeking approval in the U.S. for the following indication:

- Control and prevention of bleeding episodes (also during and after surgery) in adults and children with Hemophilia A.

The clinical pharmacokinetics of *human-cl rhFVIII* has been assessed in 5 clinical studies. GENA-01, GENA-03 and GENA-09 included a full analysis of PK parameters. In the remaining two supportive studies, GENA-04 (extension study of GENA-09) and GENA-08, only in vivo recovery (IVR) data were collected.

An overview of studies that included PK assessments of *human-cl rhFVIII* is provided in Table 1.

GENA-01 was a prospective, randomized, actively controlled, open-label, multicenter Phase 2 study in previously treated patients (PTPs) with severe hemophilia A (FVIII:C \leq 1%). This study enrolled 22 PTPs between 12 and 65 years. All patients had undergone the baseline PK assessment, for which they were randomized to receive either *human-cl rhFVIII* followed by Kogenate FS or Kogenate FS followed by *human-cl rhFVIII*. (crossover design to establish bioequivalence). In addition to the baseline PK assessment, a 3-month IVR assessment and a 6-month PK assessment were performed for *human-cl rhFVIII* only.

Blood samples for the determination of FVIII plasma levels were taken before infusion and up to 48 hours after the end of the infusion.

Table 1: Overview of studies involving PK investigations for *Human-cl rhFVIII*

	GENA-01	GENA-08	GENA-03	GENA-09	GENA-04
Patients [‡]	22 PTPs 12–65 years	32 PTPs 18–75 years	59 PTPs 2–12 years (26 for PK)	22 PTPs 18–62 years	18 PTPs who completed GENA-09
PK investigation (including IVR)	At baseline (comparator: Kogenate FS) and 6 months (only <i>Human-cl</i> <i>rhFVIII</i>)	–	At baseline (comparator: previous FVIII concentrate)	At baseline (comparator: Kogenate) and 6 months (only <i>Human-cl</i> <i>rhFVIII</i>)	–
IVR investigation only	At 3 months	At baseline, 3 and 6 months	At baseline [†] , 3 [‡] and 6 [‡] months	At 3 months	At 3 months and then 3 monthly until study end
Immunogenicity	Yes	Yes	Yes	Yes	Yes
Efficacy	Yes	Yes	Yes	Yes	Yes
Safety	Yes	Yes	Yes	Yes	Yes

[‡] All patients.

[†] Patients not participating in the PK phase of the study.

FVIII = coagulation factor VIII; IVR = in vivo recovery; PK = pharmacokinetic; PTP = previously treated patient.

Patients received a nominal dose of 50 IU/kg and blood samples were analyzed using both the one-stage clotting assay (OS) and the (b) (4) chromogenic substrate assay (CHR). PK data analysis was performed using non-compartmental methodology.

Based on the OS assay, the geometric mean ratio of the dose normalized AUC (AUC_{norm}) for *human-cl rhFVIII* compared with Kogenate FS was 0.907 and the 90% confidence interval (0.859, 1.088) was fully included within the acceptance limits of 0.8 to 1.25, indicating bioequivalence of *human-cl rhFVIII* and Kogenate FS. Similar results were obtained using the CHR assay.

OS assay based PK parameters (Mean ± SD, N = 22) for *human-cl rhFVIII* at a dose of 50 IU/kg were: T_{1/2} = 17.1 ± 11.2 h, IVR = 2.14 ± 0.27 % per IU/kg, and CL = 2.96 ± 0.97 mL/hr/kg. Similar results were obtained with the CHR assay.

Overall, the PK profile of *human-cl rhFVIII* at 6 months was generally comparable to the profile measured at study start (first dose).

For baseline, after 3 months and after 6 months of treatment with *human-cl rhFVIII*, the mean IVR values were within the range of 2.0 to 2.5 % per IU/kg

GENA-03 was a prospective, non-controlled, open label, multinational, multicenter Phase 3 study in 59 children suffering from severe hemophilia A (FVIII:C <1%), belonging to either of the two age cohorts of 30 previously treated patients (PTPs) aged 6 to 12 years, and 29 PTPs aged 2 to 5 years, all with at least 50 previous exposure days (EDs) to FVIII concentrates. Twenty-six patients underwent PK analysis with their previous FVIII concentrate and *human-cl rhFVIII*. Of these, 13 patients were between 2 and 5 years of age, and 13 were between 6 and 12 years of age. Blood samples for the determination of FVIII plasma levels were taken before infusion and 30 minutes and 2, 5, 10, 24 and 48 hours after the end of the infusion. IVR assessments were performed at baseline, and after 3 and 6 months of treatment in all patients. Pediatric patients received a nominal dose of 50 IU/kg and blood samples were analyzed using both the one-stage aPTT clotting assay (OS) and the (b) (4) chromogenic substrate assay (CHR). PK data analysis was performed using non-compartmental methodology.

For the 13 children aged 2 to 5 yr the OS assay based PK parameters (Mean \pm SD) for *human-cl rhFVIII* were: $T_{1/2} = 11.9 \pm 5.4$ h, IVR = 1.6 ± 0.2 % per IU/kg, and CL = 5.4 ± 2.3 mL/hr/kg. Similar results were obtained with the CHR assay.

For the 13 children aged 6 to 12 yr the OS assay based PK parameters (Mean \pm SD) for *human-cl rhFVIII* were: $T_{1/2} = 13.1 \pm 2.6$ h, IVR = 1.6 ± 0.4 % per IU/kg, and CL = 4.1 ± 0.9 mL/hr/kg. Similar results were obtained with the CHR assay.

For the ITT population the mean incremental IVRs according to the CHR assay ranged from 1.568–1.834% per IU/kg.

In general (for the overall population and the two age groups), values for the OS assay followed a similar pattern compared to the CHR assay. In comparison to the PK parameters in adults, the values for AUC, IVR and $T_{1/2}$ were lower and CL (based on per kg bodyweight) was higher in children. This has also been observed with other rFVIII products.

GENA-09 was a prospective, open-label, single-center Phase 2 study in previously treated patients (PTPs) with severe hemophilia A (FVIII:C \leq 1%) with a randomized crossover PK part and an uncontrolled prophylaxis part. This study enrolled 22 PTPs between 18 and 62 years at a single center in Russia. This patient population differed from other adult populations in *human-cl rhFVIII* studies in that these patients had been inadequately treated in the past.

Recovery assessments at 3 months and full PK analyses at 6 months were performed in all 22 patients who received *human-cl rhFVIII* prophylaxis.

PTPs received a nominal dose of 50 IU/kg of Kogenate or *human-cl rhFVIII*. Blood samples were analyzed using both the one-stage aPTT clotting assay (OS) and the (b) (4) chromogenic substrate assay (CHR). PK data analysis was performed using non-compartmental methodology.

Human-cl rhFVIII was found to be bioequivalent to the currently licensed recombinant FVIII comparator, Kogenate.

OS assay based PK parameters (Mean \pm SD, N = 22) for *human-cl rhFVIII* at a dose of 50 IU/kg were: $T_{1/2} = 11.43 \pm 3.94$ h, $IVR = 2.19 \pm 0.555$ % per IU/kg, and $CL = 3.94 \pm 1.44$ mL/hr/kg. Similar results were obtained with the CHR assay.

Mean incremental IVR at baseline, after 3 months, and after 6 months for *human-cl rhFVIII* was comparable between time points as determined with the OS assay (2.2, 2.1 and 2.3 % per IU/kg, respectively).

Overall, PK parameters for *human-cl rhFVIII* at 6 months were consistent with those obtained at study start (first dose).

GENA-04 was a prospective, single-center, uncontrolled, open-label, Phase 3 study in previously treated patients (PTPs) with severe hemophilia (FVIII:C $\leq 1\%$) who completed the previous study, GENA-09. Eighteen patients who completed study GENA-09 crossed into GENA-04. Only IVR was calculated at 3-monthly intervals of treatment from the FVIII levels preinfusion and the peak level obtained in the 30 and 60 minute post-infusion samples. Patients received a nominal dose of 50 IU/kg of *human-cl rhFVIII* and blood samples were analyzed using both the one-stage clotting assay (OS) and the (b) (4) chromogenic substrate assay (CHR).

For the OS assay the mean IVR over time was in the range of 1.52 to 1.84 % per IU/kg while for the CHR assay the mean IVR over time was in the range of 1.77 to 2.34 % per IU/kg. These results are consistent with the expected values. After multiple dosing results of IVR did not change.

GENA-08 was a prospective, open-label, international, multicenter Phase 3 study in previously treated patients (PTPs) with severe hemophilia A. The study enrolled 32 patients. All were males between 18 and 75 years of age.

Only IVR was calculated at study entry and after 3 and 6 months of treatment from the FVIII levels pre-infusion and the peak levels obtained in the 15, 30, 45 or 60 minutes post-infusion samples. Patients received a nominal dose of 50 IU/kg of *human-cl rhFVIII* and blood samples were analyzed using both the one-stage clotting assay (OS) and the (b) (4) chromogenic substrate assay (CHR).

For the OS assay the mean IVR over time was in the range of 2.01 to 2.20 % per IU/kg while for the CHR assay the mean IVR over time was in the range of 2.34 to 2.57 % per IU/kg. These

results are consistent with the expected values. After multiple dosing results of IVR did not change.

Reviewer's Comments:

- Key PK parameters for *human-cl rhFVIII* were largely comparable to the comparator Kogenate FS in study GENA-01. Data from GENA-01 indicate bioequivalence of *human-cl rhFVIII* with Kogenate FS measured by both assays.
- Pediatric data from GENA-03 demonstrated similar PK profiles for *human-cl rhFVIII* compared with the previously used FVIII concentrates. However, compared with data from adult studies, a higher bodyweight based CL, a shorter T_{1/2}, and lower AUC and IVR has been observed in younger patients. Similar results were obtained with data from the CHR assay.

Compared to adults, there appears to be a substantial increase in mean bodyweight adjusted systemic CL (+83%) in pediatric patients 2 to < 6 years of age. The difference between adult CL and pediatric CL (6-12 yr) was less pronounced (+37%). These differences should be taken into account when dosing children 2 to 12 years of age. Similar results were obtained with data from the CHR assay.

- PK parameters at 6 months were consistent with those obtained at study start (first dose).
- Data from GENA-09 (at 6 months) and GENA-04 (cumulative exposure in GENA-09 and GENA-04 of up to 21 months) provide supportive evidence for the comparability of IVR over time.
- The PK parameter differences between the two assay methods appear not to be of clinical significance.

OVERALL COMMENTS

- In general, all presented study designs, results, and conclusions are acceptable from Clinical Pharmacology perspective.
- Significantly higher weight-adjusted CL of *human-cl rhFVIII* has been observed in pediatric patients compared with adult patients. This should be addressed with a higher dose or higher dosing frequency for the pediatric patient group.

CLINICAL PHARMACOLOGY LABELING COMMENTS

12. CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

FDA comment: Please delete the 2nd column in Table 3. The display of PK data based on the OS assay is sufficient.

Table 1: PK parameters for Nuwiq[®] in 22 adult and adolescent PTPs with severe hemophilia A (Dose: 50 IU/kg)

PK parameter	Chromogenic assay	One-stage clotting assay
	Mean ± SD	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

12.4 Special Populations and Conditions

Higher doses and/or dosing frequency ~~may~~ **should** be considered in younger patients. ~~however, no marked differences in PK parameters have been observed between patients aged 2 to 5 years and those aged 6 to 12 years.~~

FDA comment:

1. Please suggest a pediatric dosing regimen based on CL.
2. Please delete the 2nd column in Table 4 and Table 5. The display of PK data based on the OS assay is sufficient.
3. Please combine Table 4 and Table 5 into one Table, showing pediatric PK results side-by-side for the 2 subgroups.

Table 2: PK parameters for Nuwiq® in 13 previously treated children aged 6 to 12 years with severe hemophilia A (Dose: 50 IU/kg)

PK parameter	Chromogenic assay	One-stage clotting assay
	Mean ± SD	Mean ± SD
AUC (h·IU/mL)	13.2 ± 3.4	11.8 ± 2.7
AUC _{norm} (h·IU/mL/(IU/kg))	0.3 ± 0.1	0.3 ± 0.1
C _{maxnorm} (IU/mL/(IU/kg))	0.019 ± 0.004	0.017 ± 0.004
T _{1/2} (h)	10.0 ± 1.9*	13.1 ± 2.6 [#]
IVR (%/IU/kg)	1.9 ± 0.4	1.6 ± 0.4
MRT (h)	12.7 ± 2.3	16.5 ± 2.9
CL (mL/h/kg)	4.3 ± 1.2	4.1 ± 0.9
V _{ss} (mL/kg)	54.5 ± 14.8	66.1 ± 16.0

Table 3: PK parameters for Nuwiq® in 13 previously treated children aged 2 to 5 years with severe hemophilia A (Dose: 50 IU/kg)

PK parameter	Chromogenic assay	One-stage clotting assay
	Mean ± SD	Mean ± SD
AUC (h·IU/mL)	11.7 ± 5.3	10.1 ± 4.6
AUC _{norm} (h·IU/mL/(IU/kg))	0.2 ± 0.1	0.2 ± 0.1
C _{maxnorm} (IU/mL/(IU/kg))	0.019 ± 0.003	0.016 ± 0.002
T _{1/2} (h)	9.5 ± 3.3*	11.9 ± 5.4 [#]
IVR (%/IU/kg)	1.9 ± 0.3	1.6 ± 0.2
MRT (h)	11.9 ± 4.9	15.1 ± 7.4
CL (mL/h/kg)	5.4 ± 2.4	5.4 ± 2.3
V _{ss} (mL/kg)	55.3 ± 7.1	68.3 ± 10.4

RECOMMENDATION

The study design, results, and conclusions of the pharmacokinetic studies of *human-cl rhFVIII* are acceptable. Recommended changes to the package insert should be addressed by the applicant.

Carl-Michael Staschen, M.D., Ph.D.
Clinical Pharmacology Reviewer
Division of Hematology Clinical Review
Office of Blood Review & Research

Iftexhar Mahmood, Ph.D.
Senior Clinical Pharmacology Reviewer
Division of Hematology Clinical Review
Office of Blood Review & Research

Anne Pilaro, Ph.D.
Acting Branch Chief
Division of Hematology Clinical Review
Office of Blood Review & Research

Introduction/Background

Coagulation factor FVIII is a normal constituent of human plasma and is predominantly produced in the liver, but also by other tissues such as the kidney, lymph nodes or spleen and if not utilized within coagulation events degraded by the mononuclear phagocyte system. FVIII circulates in the plasma non-covalently bound to VWF.

Hemophilia A is an inherited sex-linked disorder of blood coagulation in which affected males do not produce functional coagulation FVIII in sufficient quantities to achieve satisfactory

hemostasis. The incidence of congenital hemophilia A is approximately 1 in 10,000 births.

Disease severity is classified according to the level of FVIII activity (% of normal) as mild (>5% to <40%), moderate (1% to 5%) or severe (<1%). Due to deficiencies in FVIII, patients with hemophilia A are predisposed to recurrent bleeding episodes (BEs). Most BEs occur in joints and muscles. Without adequate treatment these repeated hemarthroses and hematomas lead to long-term sequelae with severe disability. Other less frequent, but more severe bleeding sites, are the central nervous system, the urinary or gastrointestinal tract, eyes and the retro-peritoneum.

Patients with hemophilia A are at high risk of developing major and life-threatening bleeds after surgical procedures, even after minor procedures such as tooth extraction. The optimal effective treatment of the disorder is replacement of FVIII using FVIII concentrate either obtained by fractionation of human plasma or manufactured by recombinant DNA technology.

Octapharma is developing a recombinant human coagulation factor VIII (rhFVIII) for the treatment of hemophilia A. *Human-cl rhFVIII* (human cell line rhFVIII) is a fourth-generation B-domain-deleted rFVIII expressed in genetically modified human embryonic kidney (HEK) 293F cells. The deleted B-domain (b) (4) The harvested product is concentrated and purified by a series of chromatography steps. No animal proteins are used in the purification process and no human albumin is used as a stabilizer in the manufacture of *human-cl rhFVIII*. The manufacturing process also includes solvent/detergent (S/D) treatment and nanofiltration steps for virus inactivation/removal. *Human-cl rhFVIII* drug product consists of a white to off-white sterile lyophilized powder and a solvent to prepare a solution for injection. The lyophilized powder is supplied in vials containing 250 IU, 500 IU, 1000 IU or 2000 IU rhFVIII per vial, to be reconstituted with 2.5 mL of water for injection. The reconstituted solution is a clear, colorless solution, containing 100 IU / 200 IU / 400 IU / 800 IU FVIII:C/mL.

The company is seeking approval in the U.S. for the following indication:

- *Human-cl rhFVIII* (Nuwiq®) is indicated for the control and prevention of bleeding episodes (also during and after surgery) in adults and children with Hemophilia A.

The clinical pharmacokinetics of *human-cl rhFVIII* (rhVIII) has been assessed in 5 clinical studies. GENA-01, GENA-03 and GENA-09 included a full analysis of PK parameters. In the

remaining two supportive studies, GENA-04 (extension study of GENA-09) and GENA-08, only in vivo recovery (IVR) data were collected.

1. Study Title: 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 hemophilia A. Study report GENA-01.

Objectives:

Primary Objective:

- 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 previously treated patients (PTPs) suffering from severe hemophilia A.

Secondary Objectives:

- 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 bleeding episodes (BEs)
- To assess clinical efficacy and safety of *human-cl rhFVIII* in surgical prophylaxis

Study Design:

This study enrolled 22 patients between 12 and 65 years from 9 centers in Germany, Bulgaria and the USA. All patients had undergone the baseline PK assessment, for which they were randomized to receive either *human-cl rhFVIII* followed by Kogenate FS or Kogenate FS followed by *human-cl rhFVIII*. Based on discussions with the FDA, a single product (Kogenate FS) was used as the comparator and formal bioequivalence analyses were performed. In addition to the baseline PK assessment, a 3-month IVR assessment and a 6-month PK assessment were performed for *human-cl rhFVIII* only.

Patients received a nominal dose of 50 IU/kg for both, the initial PK assessment and for the 6-month PK assessment of *human-cl rhFVIII*. The drug was to be administered as an intravenous bolus injection at a maximum speed of 4 mL/minute. Blood samples for the determination of FVIII plasma levels were taken before infusion and at 15, 30 and 45 minutes and 1, 3, 6, 9, 12, 24, 30 and 48 hours after the end of the infusion. For IVR analysis at 3 months blood samples were taken before infusion and at 15, 30, 45 and 60 minutes after the end of the infusion.

Blood samples were analyzed using both a one-stage aPTT clotting assay (OS) and a (b) (4) chromogenic substrate assay (CHR). PK data analysis was performed using non-compartmental methodology.

Results:

Part 1. Bioequivalence: Comparison with Kogenate FS

Results are presented for all 22 patients of the PK per-protocol (PK-PP) population. PK data as determined by the CHR and OS assays are summarized in Table 1 and Table 2. FVIII:C over time was virtually identical for both concentrates and both assays; however, values observed for FVIII values over time with the OS assay were generally lower than those determined by the CHR assay.

The mean values for the dose normalized AUC for FVIII:C as measured by the CHR and OS assays following administration of 50 IU/kg for *human-cl rhFVIII* and for Kogenate FS are shown in Table 1.

Table 1: Comparative ANOVA Results for AUC_{norm} (h·IU/mL/[IU/kg]) PK-PP Population, N=22)

Assay	Treatment	Mean	SD	Ratio of geometric means†	90% CI
CHR	<i>Human-cl rhFVIII</i>	0.39	0.14	0.98	0.874, 1.107
	Kogenate FS	0.38	0.09		
OS	<i>Human-cl rhFVIII</i>	0.37	0.11	0.97	0.859, 1.088
	Kogenate FS	0.38	0.10		

† For *Human-cl rhFVIII* compared with Kogenate.

ANOVA = analysis of variance; AUC_{norm} = area under the curve normalized to the dose administered;

CHR = chromogenic; CI = confidence interval; IU = international units; N = number of patients;

OS = one-stage; PK = pharmacokinetic; PP = per-protocol; SD = standard deviation.

The geometric mean ratios of AUC Kogenate FS were around 1 and the 90% within the usual acceptance limits of 0.8 to 1.25, indicating bioequivalence of *human-cl rhFVIII* and Kogenate FS.

Data for secondary PK parameters for *human-cl rhFVIII* and Kogenate FS measured by the CHR and OS assays are shown in Table 2.

PK profiles of *human-cl rhFVIII* and its licensed comparator Kogenate FS were generally comparable. No significant differences in parameter values were detected between the CHR and the OS assay.

Part 2. PK at 6 months.

PK parameters after *human-cl rhFVIII* administration were also examined 6 months after the study start in 21 patients. The majority of the PK parameters were similar at 6 months compared to study start. The mean FVIII:C plasma concentration after 6 months were nearly identical to those at the beginning of the study, both for the CHR and the OS assays.

Table 2: Secondary PK results (Mean±SD) (PK-PP Population, N=22)

Parameter	Assay	Mean ± SD	
		<i>Human-cl rhFVIII</i>	Kogenate FS
AUC (h·IU/mL)	CHR	22.5 ± 7.8	21.3 ± 4.7
	OS	18.0 ± 5.6	24.2 ± 6.0
C _{max} (IU/mL)	CHR	1.46 ± 0.22	1.39 ± 0.20
	OS	1.05 ± 0.15	1.31 ± 0.18
C _{maxnorm} (IU/mL/[IU/kg])	CHR	0.025 ± 0.004	0.025 ± 0.003
	OS	0.022 ± 0.003	0.021 ± 0.003
IVR (% per IU/kg)	CHR	2.50 ± 0.37	2.49 ± 0.32
	OS	2.14 ± 0.27	2.03 ± 0.28
T _{max} (h)	CHR	0.35 ± 0.23	0.34 ± 0.20
	OS	0.43 ± 0.28	0.41 ± 0.27
T _{1/2} (h)	CHR	14.7 ± 10.0	16.1 ± 5.9
	OS	17.1 ± 11.2	18.8 ± 5.9
MRT (h)	CHR	19.5 ± 12.0	20.0 ± 5.6
	OS	22.5 ± 14.2	24.2 ± 6.8
CL (mL/h/kg)	CHR	2.94 ± 1.18	2.75 ± 0.64
	OS	2.96 ± 0.97	2.82 ± 0.72
V _{ss} (mL/kg)	CHR	49.6 ± 17.3	53.3 ± 13.6
	OS	59.8 ± 19.8	64.8 ± 12.8

AUC = area under the curve; AUC_{norm} = area under the curve normalized to the dose administered; CHR = chromogenic; CL = clearance; C_{max} = maximum plasma concentration; C_{maxnorm} = maximum plasma concentration normalized to the dose administered; IU = international units; IVR = in vivo recovery; MRT = mean residence time; N = number of patients; OS = one-stage; PK = pharmacokinetic; PP = per-protocol; SD = standard deviation; T_{1/2} = half-life; T_{max} = time to maximum plasma concentration; V_{ss} = volume of distribution at steady state

When measured with the OS assay only, the mean AUCnorm was lower and the mean CL higher than at study start. Upon analysis of the PK data at 6 months, unusually low AUCnorm ratios (6-month vs initial PK) were observed in 3 Bulgarian patients, which were not seen in the other patients and had not been observed in previous studies with *human-cl rhFVIII*. Consequently, an exploratory analysis excluding all 6 patients from the Bulgarian center was performed. When the data were analyzed without the patients from the Bulgarian center, all PK parameters were comparable between 6 months and at study start.

When the patients from the Bulgarian center were taken out of the analysis, all PK parameters were similar between 6 months and study start. At 6 months, the mean AUCnorm was 0.35±0.11 h·IU/mL/(IU/kg), the mean T_{1/2} was 14.57±5.06 h and the mean CL was 3.13±1.11 mL/h/kg.

IVR Results over Time

All 22 patients in the intention-to-treat (ITT) population underwent IVR analysis at study entry and 3 and 6 months after start of on-demand treatment. Results from these analyses are shown in Table 3.

Table 3: IVR (%/IU/kg) for *human-cl rhFVIII* at study entry and 3- and 6-months after the start of on-demand treatment (ITT Population, N=22).

Time point	Parameter	Mean	SD	Median	Range
Study entry (Part I)	CHR assay	2.50	0.37	2.46	1.668–3.150
	OS assay	2.14	0.27	2.13	1.713–2.787
3 months*	CHR assay	2.44	0.56	2.49	1.607–3.629
	OS assay	2.06	0.39	2.05	1.482–3.106
6 months	CHR assay	2.34	0.50	2.41	1.338–3.785
	OS assay	2.01	0.33	1.98	1.375–2.680

* N=20; Two patients did not have any values for IVR at this time point.

CHR = chromogenic; ITT = intention-to-treat; IU = international units; IVR = in vivo recovery; OS = one-stage; SD = standard deviation.

The mean IVR values were within the range of 2.0 to 2.5 %/IU/kg. Values obtained by the OS assay were generally lower than those obtained with the CHR assay. Mean recoveries at 3 and at 6 months tended to be slightly lower than those at study entry; however, the values still remained high and within the range of 2.0 to 2.5 %/IU/kg with both assays.

Conclusion:

- *Human-cl rhFVIII* and marketed FVIII product Kogenate FS were shown to be bioequivalent.
- All PK parameters including IVR were comparable between single and repeat dosing (after removing patients from the Bulgarian center out of the analysis).

2. Study Title: Prospective clinical study in children with severe hemophilia A to investigate clinical efficacy, immunogenicity, pharmacokinetics, and safety of *human-cl rhFVIII*.

Study report GENA-03.

Objectives:

To assess clinical efficacy of *human-cl rhFVIII* in terms of prevention and treatment of (breakthrough) bleeding episodes (BEs).

Primary:

- To determine pharmacokinetics (PK) of *human-cl rhFVIII*

Secondary:

- 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 adverse event (AE) monitoring.

Study Design:

This was a prospective, non-controlled, open label, multinational, multicenter phase III study in 59 children suffering from severe hemophilia A (FVIII:C <1%), belonging to either of the two age cohorts of

- 30 previously treated patients (PTPs) aged 6 to 12 years, and
- 29 PTPs aged 2 to 5 years

all with at least 50 previous exposure days (EDs) to FVIII concentrates.

Twenty-six (26) patients participated in the PK phase of the study in which they received their previous FVIII concentrate (pdFVIII or full-length rFVIII) followed by *human-cl rhFVIII* in a non-randomized crossover design. Of these 26 patients, 13 patients were between 2 and 5 years of age, and 13 were between 6 and 12 years of age. An additional 32 patients did not participate in the PK phase, but had an initial IVR assessment. IVR assessments were also performed after 3 and 6 months of treatment in all patients.

Human-cl rhFVIII was administered at the dose of 50 IU/kg BW for PK and IVR assessments in Part 1 and Part 2. For prophylactic treatment in Part 2, 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. Blood samples for the determination of FVIII plasma levels were taken before infusion and 30 minutes and 2, 5, 10, 24 and 48 hours after the end of the infusion. The IVR of *human-cl rhFVIII* was calculated from the FVIII plasma level pre-infusion and the peak level obtained in the 30 minutes or 2 hours post-infusion samples.

Blood samples were analyzed using both the one-stage aPTT clotting assay (OS) and the (b) (4) chromogenic substrate assay (CHR). PK data analysis was performed using non-compartmental methodology (WinNonlin, Version 5.2).

Results

PK parameters are presented for patients between 2 and 5 years (N=13) and between 6 and 12 years (N=13) in Table 1 and Table 2, respectively. For major PK parameters values for the OS assay followed a similar pattern to the CHR assay.

Table 1: PK results (Mean±SD) in age group 2 to 5 years (N=13)

Parameter	Assay*	Mean SD	
		<i>Human-cl rhFVIII</i>	Previous FVIII
AUC (h·IU/mL)	CHR	11.69 ± 5.30	8.68 ± 3.00
	OS	10.07 ± 4.60	10.83 ± 3.41
AUC _{norm} (h·IU/mL/[IU/kg])	CHR	0.22 ± 0.10	0.20 ± 0.06
	OS	0.22 ± 0.10	0.21 ± 0.06
C _{max} (IU/mL)	CHR	0.992 ± 0.148	0.746 ± 0.116
	OS	0.729 ± 0.088	0.797 ± 0.120
C _{maxnorm} (IU/mL/[IU/kg])	CHR	0.019 ± 0.003	0.017 ± 0.002
	OS	0.016 ± 0.002	0.015 ± 0.002
IVR (% per IU/kg)	CHR	1.871 ± 0.270	1.683 ± 0.224
	OS	1.572 ± 0.167	1.513 ± 0.222
T _{max} (h)	CHR	0.50 ± 0.00	0.75 ± 0.58
	OS	0.50 ± 0.00	0.73 ± 0.56
T _{1/2} (h)	CHR	9.49 ± 3.32	10.07 ± 2.90
	OS	11.91 ± 5.36	11.74 ± 3.03
MRT (h)	CHR	11.92 ± 4.93	12.35 ± 3.68
	OS	15.11 ± 7.35	15.03 ± 4.31
CL (mL/h/kg)	CHR	5.40 ± 2.37	5.65 ± 2.01
	OS	5.41 ± 2.32	5.23 ± 1.68
V _{ss} (mL/kg)	CHR	55.32 ± 7.09	64.08 ± 9.60
	OS	68.29 ± 10.42	73.37 ± 16.53

* Analyzed population n=12 for CHR assay for previous FVIII concentrate.

AUC = area under the curve; AUC_{norm} = area under the curve normalized to the dose administered; CHR = chromogenic; C_{max} = maximum plasma concentration; C_{maxnorm} = maximum plasma concentration normalized to the dose administered; CL = clearance; IU = international units; IVR = in vivo recovery; MRT = mean residence time; N = number of patients; OS = one-stage; PK = pharmacokinetics; PP = per-protocol; SD = standard deviation; T_{1/2} = half-life; T_{max} = time to maximum plasma concentration; V_{ss} = volume of distribution at steady state.

Table 2: PK Results (Mean±SD) in age group 6 to 12 years (N=13)

Parameter	Assay*	Mean SD	
		<i>Human-cl rhFVIII</i>	Previous FVIII
AUC (h·IU/mL)	CHR	13.15 ± 3.43	12.69 ± 5.18
	OS	11.77 ± 2.72	15.62 ± 5.35
AUC _{norm} (h·IU/mL/[IU/kg])	CHR	0.25 ± 0.06	0.28 ± 0.09
	OS	0.26 ± 0.06	0.29 ± 0.09
C _{max} (IU/mL)	CHR	1.017 ± 0.225	0.903 ± 0.346
	OS	0.776 ± 0.164	0.911 ± 0.253
C _{maxnorm} (IU/mL/[IU/kg])	CHR	0.019 ± 0.004	0.020 ± 0.006
	OS	0.017 ± 0.004	0.017 ± 0.004
IVR (% per IU/kg)	CHR	1.881 ± 0.440	2.000 ± 0.564
	OS	1.641 ± 0.377	1.669 ± 0.355
T _{max} (h)	CHR	0.63 ± 0.43	0.73 ± 0.56
	OS	0.62 ± 0.42	0.73 ± 0.56
T _{1/2} (h)	CHR	9.99 ± 1.88	11.94 ± 1.73
	OS	13.08 ± 2.59	14.51 ± 2.41
MRT (h)	CHR	12.74 ± 2.34	14.95 ± 2.40
	OS	16.53 ± 2.87	18.82 ± 3.32
CL (mL/h/kg)	CHR	4.33 ± 1.21	3.93 ± 1.41
	OS	4.05 ± 0.92	3.69 ± 1.09
V _{ss} (mL/kg)	CHR	54.45 ± 14.80	56.92 ± 16.42
	OS	66.07 ± 15.99	67.28 ± 15.01

* Analyzed population n=12 for CHR assay for *Human-cl rhFVIII*.

AUC = area under the curve; AUC_{norm} = area under the curve normalized to the dose administered; CHR = chromogenic; C_{max} = maximum plasma concentration; C_{maxnorm} = maximum plasma concentration normalized to the dose administered; CL = clearance; IU = international units; IVR = in vivo recovery; MRT = mean residence time; N = number of patients; OS = one-stage; PK = pharmacokinetics; PP = per-protocol; SD = standard deviation; T_{1/2} = half-life; T_{max} = time to maximum plasma concentration; V_{ss} = volume of distribution at steady state

In the overall population and for both assays, the mean values for AUC_{norm}, IVR, CL and T_{1/2} of both groups were similar. Dose adjusted mean AUC_{norm} was lower (0.22 vs 0.25 hr·IU/mL/[IU/kg]) and mean T_{1/2} shorter (9.49 vs 9.99 h) in children aged 2 to 5 years in comparison to children aged 6 to 12 years, respectively, as measured with the CHR assay. The same trend was observed when the OS assay was used (AUC_{norm}: 0.22 vs 0.26 hr·IU/mL/[IU/kg] and T_{1/2}: 11.91 vs 13.08 h).

A comparison of the two subgroups defined by age shows lower AUC_{norm} and IVR, shorter T_{1/2} and higher CL in the 2 to 5 years age group as compared with the 6 to 12 years age group. These differences are seen independently of the assay used and can most probably be attributed to differences in FVIII CL due to metabolic differences in younger patients.

IVR Results over Time

Data using the OS assay for the whole ITT population are shown in Table 3.

Table 3: IVR Values (%/IU/kg) for *human-cl rhFVIII* (OS assay) over time for all patients and for the two age subgroups (ITT Population)

Time point	Parameter	Mean	SD	Median	Range
Start of study, Phase I*	All patients (n=27)	1.575	0.327	1.594	0.748–2.239
	Aged 2–5 (n=13)	1.572	0.167	1.602	1.215–1.874
	Aged 6–12 (n=14)	1.577	0.434	1.519	0.748–2.239
Start of study, Phase II*	All patients (n=31)†	1.419	0.357	1.454	0.650–2.159
	Aged 2–5 (n=16)	1.321	0.309	1.408	0.650–1.732
	Aged 6–12 (n=15)†	1.523	0.385	1.528	0.666–2.159
3 months	All patients (n=53)**	1.470	0.359	1.504	0.810–2.345
	Aged 2–5 (n=29)	1.350	0.268	1.388	0.810–1.747
	Aged 6–12 (n=24)**	1.615	0.405	1.628	0.854–2.345
6 months	All patients (n=55)‡‡	1.525	0.343	1.501	0.823–2.580
	Aged 2–5 (n=28)†	1.441	0.296	1.456	0.823–2.096
	Aged 6–12 (n=27)††	1.611	0.371	1.577	1.109–2.580

† Data not available for 1 patient; †† Data not available for 3 patients; ‡‡ Data not available for 4 patients; ** Data not available for 6 patients; Data were not available for 2 patients (6–12 years) at 3 and 6 months due to premature withdrawal from the study; other missing IVR values were not evaluable.

* Phase I includes all patients who underwent PK analysis in Cycles 1 and 2; Phase II specifies recovery at start of open treatment phase and therefore only patients who did not undergo PK.

ITT = intention-to-treat; IU = international units; IVR = in vivo recovery; OS = one-stage; PK = pharmacokinetics; SD = standard deviation.

For the OS assay, mean IVR values in the ITT population ranged from 1.419 to 1.575 overall, from 1.321 to 1.572 in patients aged 2–5 years and from 1.523 to 1.615 in patients aged 6–12 years. In the PK-PP population, mean IVR values ranged from 1.466 to 1.607%/IU/kg overall, from 1.368 to 1.572%/IU/kg in patients aged 2–5 years and from 1.546 to 1.641 in patients aged 6–12 years. Similar results were obtained using the CRH assay,

Applicant's Conclusions:

- In general, PK parameters for *human-cl rhFVIII* and the previously used concentrates were comparable, across all assessments.

- In comparison to the PK parameters in adults, the values for AUC_{norm}, IVR and T_{1/2} were lower and bodyweight adjusted CL was higher in children. This has also been observed with other rFVIII products.

3. Study Title: Clinical study to investigate the pharmacokinetics, efficacy, safety and immunogenicity of human-cl rhFVIII in previously treated patients with severe hemophilia A. Study report GENA-09.

Objectives

Primary objective:

- To determine the PK profile of Human-cl rhFVIII in terms of the FVIII coagulant activity (FVIII:C) and to compare it with the FVIII:C profile of Kogenate in PTPs with severe hemophilia A (FVIII:C $\leq 1\%$).

Secondary objectives:

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

Study Design:

This study enrolled 22 PTPs between 18 and 62 years at a single center in Russia. This patient population differs from other adult populations in *human-cl rhFVIII* studies in that these patients had been inadequately treated in the past. Patients were randomized to receive either *human-cl rhFVIII* followed by Kogenate or Kogenate followed by *human-cl rhFVIII* for the initial PK assessment. Patients subsequently received prophylaxis treatment with *human-cl rhFVIII*, every other day, for 6 months. After 3 months, IVR of *human-cl rhFVIII* was determined.

A second PK assessment (*human-cl rhFVIII* only) was performed after 6 months. All PK assessments were performed after a wash-out phase of at least 96 hours. Blood samples for the determination of FVIII levels were taken before infusion and at 15, 30 and 45 minutes and 1, 3, 6, 9, 12, 24, 30 and 48 hours after the end of the infusion. The infusion for IVR assessment was administered after a wash-out phase of at least 48 hours before the infusion. FVIII plasma level pre-infusion and the peak levels obtained in the 15, 30, 45 or 60 minutes post-infusion samples were used for the calculation.

PK data analysis was performed using non-compartmental methodology.

PK Results

Results are presented for the 22 patients of the PP population, which was identical to the ITT population in this study.

Human-cl rhFVIII was found to be bioequivalent to the currently licensed recombinant FVIII comparator, Kogenate. The ratio (*human-cl rhFVIII* relative to Kogenate) of geometric mean [90% CI] for the dose normalized AUC was 0.885 [0.819, 0.956] and was within the required bioequivalence range of 0.8 to 1.25.

PK data as determined by the CHR and OS assays are summarized in Table 1.

Table 1: PK Results (Mean±SD), N=22

Parameter	Assay*	Mean SD	
		<i>Human-cl rhFVIII</i>	Kogenate
AUC (h·IU/mL)	CHR	14.73 ± 5.97	17.95 ± 6.09
	OS	11.75 ± 5.22	19.85 ± 6.90
AUC _{norm} (h·IU/mL/[IU/kg])	CHR	0.29 ± 0.12	0.33 ± 0.11
	OS	0.29 ± 0.13	0.37 ± 0.13
C _{max} (IU/mL)	CHR	1.097 ± 0.159	1.199 ± 0.216
	OS	0.889 ± 0.230	1.159 ± 0.198
C _{maxnorm} (IU/mL/[IU/kg])	CHR	0.022 ± 0.003	0.022 ± 0.004
	OS	0.022 ± 0.005	0.021 ± 0.004
IVR (% per IU/kg)	CHR	2.172 ± 0.281	2.166 ± 0.393
	OS	2.190 ± 0.555	2.111 ± 0.386
T _{max} (h)	CHR	0.38 ± 0.20	0.49 ± 0.26
	OS	0.38 ± 0.21	0.38 ± 0.19
T _{1/2} (h)	CHR	11.11 ± 2.98	13.45 ± 3.39
	OS	11.43 ± 3.94	16.16 ± 5.88
MRT (h)	CHR	14.68 ± 4.10	17.62 ± 4.57
	OS	15.80 ± 5.63	21.52 ± 7.56
CL (mL/h/kg)	CHR	3.86 ± 1.39	3.38 ± 1.09
	OS	3.94 ± 1.44	3.06 ± 1.06
V _{ss} (mL/kg)	CHR	52.25 ± 10.72	55.77 ± 10.42
	OS	55.82 ± 8.94	59.41 ± 9.62

AUC = area under the curve; AUC_{norm} = area under the curve normalized to the dose administered; CHR = chromogenic; C_{max} = maximum plasma concentration; C_{maxnorm} = maximum plasma concentration normalized to the dose administered; CL = clearance; IU = international units; IVR = in vivo recovery; MRT = mean residence time; N = number of patients; OS = one-stage; PK = pharmacokinetics; PP = per-protocol; SD = standard deviation; T_{1/2} = half-life; T_{max} = time to maximum plasma concentration; V_{ss} = volume of distribution at steady state.

PK parameters were comparable between the two products. Mean values for AUC were lower for *human-cl rhFVIII* for both assays, particularly the OS assay; however, these differences were

reduced after standardization to the administered dose (AUCnorm). IVR and CL were higher for *human-cl rhFVIII* compared with Kogenate for both assays. T1/2 was shorter according to both assays, but was within the range expected for rFVIIIs.

PK Results over Time (after 6 months)

Overall, PK parameters for *human-cl rhFVIII* at 6 months were consistent with those obtained at study start (first dose).

Mean IVR for *human-cl rhFVIII* at study start and at 3 and 6 months is shown in Table 2.

Table 2: IVR values (%/IU/kg) over time (N=22)

Time point	Assay	Mean	SD	Median	Range
Study start	CHR	2.17	0.28	2.10	1.77–3.06
	OS	2.19	0.56	2.11	1.35–3.82
3 months	CHR	2.09	0.44	2.07	1.28–3.39
	OS	1.73	0.32	1.73	1.21–2.87
6 months*	CHR	2.29	0.57	2.11	1.36–3.80
	OS	1.97	0.50	1.89	1.15–3.50

* N=21.

CHR = chromogenic; ITT = intention-to-treat; IVR = in vivo recovery; N = number of patients; OS = one-stage; SD = standard deviation.

Mean and median IVRs were comparable for both assays at study start; at 3 and 6 months and the means ranged between 2.19 and 1.97 %/IU/kg). Values obtained with the OS assay were lower than those obtained with the CHR assay. Nevertheless, the results confirm no marked changes in IVR of *human-cl rhFVIII* over time.

Conclusion:

- *Human-cl rhFVIII* and marketed FVIII product Kogenate FS were shown to be bioequivalent.
- All PK parameters including IVR were similar between 6 months and study start (after removing patients from the Bulgarian center out of the analysis).

4. Study Title: Clinical study to investigate the long-term safety and efficacy of *Human-cl rhFVIII* in previously treated patients with severe Hemophilia A.
Study report GENA-04.

Objectives:

Primary objectives:

- To investigate the long-term immunogenic potential of *Human-cl rhFVIII*
- To assess the long-term tolerability of *Human-cl rhFVIII*

Secondary objectives:

- To determine the long-term efficacy of *Human-cl rhFVIII* during prophylactic treatment, in treatment of bleeding episodes (BEs) and in surgical prophylaxis in previously treated patients (PTPs) suffering from severe hemophilia A
- To calculate the long-term incremental recovery of factor VIII coagulant activity (FVIII:C) for *Human-cl rhFVIII*

Study Design

GENA-04 was the extension study of GENA-09. Of the 22 patients enrolled in the parent study, 18 enrolled in the extension study. Only IVR was assessed at 3 months and subsequently every 3 months until study completion. The IVR was calculated after a wash-out phase of at least 72 hours before the infusion. FVIII plasma level pre-infusion and the peak level obtained in the 30 or 60 minutes post infusion samples were used for the calculation. Patients received a nominal dose of 50 IU/kg and blood samples were analyzed using both the one-stage clotting assay (OS) and the (b) (4) chromogenic substrate assay (CHR).

IVR Results over Time

All 18 patients underwent at least one IVR assessment and were included in the analysis. Results for IVR over time are summarized in Table 1.

For both assays, FVIII:C profiles at the beginning and at the end of the study were nearly identical, and mean and median IVR values for both assays were also very similar at both times. However, both FVIII:C and IVR values based on the OS assay were lower than those obtained with the CHR assay. For the OS assay the mean IVR was in the range of 1.52 to 1.84 %/IU/kg while for the CHR assay the mean IVR was in the range of 1.77 to 2.34 %/IU/kg. These data indicate no significant change of IVR even over a long time period: taking into account the at least 6 months pre-treatment in GENA-09, with most patients having received *human-cl rhFVIII* for more than 18 months.

Table 1: IVR Values (%IU/kg) for *human-cl rhFVIII* over time

Time point	Assay	Mean	SD	Median	Range
Baseline* (N=18)	CHR	2.024	0.680	1.950	0.067–3.354
	OS	1.715	0.525	1.737	0.151–2.794
3 months (N=17)	CHR	2.344	0.466	2.295	1.458–3.272
	OS	1.832	0.308	1.809	1.212–2.542
6 months (N=17)	CHR	2.396	0.455	2.349	1.646–3.525
	OS	1.836	0.304	1.838	1.344–2.406
9 months (N=16)	CHR	2.210	0.529	2.170	1.316–3.669
	OS	1.688	0.343	1.693	1.032–2.430
12 months (N=16)	CHR	1.767	0.311	1.901	1.162–2.193
	OS	1.523	0.346	1.519	0.949–2.366
15 months (N=6)	CHR	1.894	0.293	1.892	1.518–2.223
	OS	1.661	0.307	1.766	1.282–1.981
Completion (N=16)	CHR	2.023	0.483	1.992	1.382–3.138
	OS	1.699	0.382	1.672	0.940–2.426

* IVR results at the end of GENA-09 were used as baseline values for GENA-04.

CHR = chromogenic; IU = international units; IVR = in vivo recovery; N = number of patients;

OS = one-stage; SD = standard deviation.

5. Study Title: Clinical study to investigate the efficacy, safety, and immunogenicity of *human-cl rhFVIII* in previously treated patients with severe hemophilia A.

Study report GENA-08.

Objectives:

Primary objective

- To determine in previously treated patients (PTPs) with severe hemophilia A the efficacy of *Human-cl rhFVIII* during prophylactic treatment, in the treatment of bleeding episodes and in surgical prophylaxis.

Secondary objectives:

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

Study design:

This study enrolled 32 PTPs of at least 12 years of age (actual age range 18–75 years) from 11 study centers in Austria, Bulgaria, Germany and the UK. The IVR of *human-cl rhFVIII* was assessed at baseline (visit 1) and after 3 and 6 months of treatment. IVR was calculated from the FVIII plasma level pre-infusion and the peak level obtained in the 15, 30, 45 or 60 minutes post-infusion samples. The wash-out periods as required per protocol were at least 72 hours for the baseline investigation and at least 48 hours for the investigations at 3 and 6 months.

IVR Results over Time

Table 1 lists the IVR results obtained for the 32 patients included in the ITT population.

Table 1: IVR values (%/IU/kg) for *human-cl rhFVIII* over time

Time point	Assay	Mean	SD	Median	Range
Visit 1 (n=32)	CHR	2.57	0.54	2.61	1.46–3.68
	OS	2.20	0.47	2.17	1.33–3.25
3 months (n=31)	CHR	2.37	0.50	2.29	1.36–3.54
	OS	2.05	0.35	2.00	1.39–2.58
6 months (n=30)	CHR	2.34	0.40	2.35	1.63–3.08
	OS	2.01	0.30	1.93	1.43–2.81

Data are % per IU/kg.

CHR = chromogenic; ITT = intention-to-treat; IVR = in vivo recovery; N = number of patients; n = number of patients in subgroup; OS = one-stage; SD = standard deviation.

Both mean and median IVRs were slightly lower at 3 and 6 months compared with baseline. IVR values based on the OS assay were lower than those obtained with the CHR assay. For the OS

assay the mean IVR over time was in the range of 2.01 to 2.20 %/IU/kg while for the CHR assay the mean IVR over time was in the range of 2.34 to 2.57 %/IU/kg. These results are consistent with the expected values. Results of IVR over time were stable.

Reviewer's Comments:

- PK parameters for *human-cl rhFVIII* were largely comparable to the comparator Kogenate FS in study GENA-01. Data from GENA-01 indicate bioequivalence of *human-cl rhFVIII* with Kogenate FS measured by both assays. Pediatric data from GENA-03 demonstrated similar PK profiles for *human-cl rhFVIII* compared with the previously used FVIII concentrates. However, compared with data from adult studies, a higher bodyweight adjusted CL, a shorter T_{1/2}, and lower AUC and IVR has been observed in younger patients. Similar results were obtained with data from the CHR assay.
- Compared to adults, there appears to be a substantial increase in mean bodyweight adjusted systemic CL (+83%) in pediatric patients 2 to < 6 years of age. The difference between adult CL and pediatric CL (6-12 yr) was less pronounced (+37%). These differences should be taken into account when dosing children 2 to 12 years of age.
- PK parameters at 6 months were examined in GENA-01 and GENA-09, and in general, were shown to be consistent with those obtained at study start (after exclusion of all 6 patients from the Bulgarian center (GENA-01)). Except unusually low PK parameters no further explanation for the exclusion was provided.
- Data from GENA-09 (at 6 months) and GENA-04 (cumulative exposure in GENA-09 and GENA-04 of up to 21 months) provide supportive evidence for the stability of IVR over time.
- The PK parameter differences between the two assay methods appear not to be of clinical significance.