EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 May 2017
EMA/331905/2017
Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Nuwiq

simoctocog alfa

Procedure no: EMEA/H/C/002813/P46/005

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Table of contents

1. Introduction

On 8th December 2016, the MAH submitted the final study report of paediatric study GENA-13 (eCTD 0041) in accordance with Article 46 of Regulation (EC) No. 1901/2006. On 18th of January 2017, GENA-13 study report - Module 2.5 was subsequently provided (eCTD 0042). No amendments to be introduced to the product information have been identified by the marketing-authorisation holder (MAH).

2. Scientific discussion

2.1. Information on the development program

The pediatric study GENA-13 was performed to investigate the long-term immunogenicity, tolerability, and efficacy of prophylactic *Human-cl rhFVIII* in previously treated children with severe haemophilia A (FVIII:C <1%). This study was a prospective, open-label, uncontrolled, international, multicenter phase 3b continuation study of the GENA-03 study. Studies GENA-01, GENA-08 and GENA-03 were the pivotal studies and study GENA-09, and its extension GENA-04 were supportive studies, mainly for assessment of inhibitor development and surgical prophylaxis. All these studies of the development program enrolled patients who were previously treated (defined as having ≥150 exposure days [EDs] in patients ≥12 years of age, and ≥50 EDs in patients <12 years of age) and the study duration per patient was the same in all studies – at least 6 months and at least 50 EDs. Identical objective measures were used to assess haemostatic efficacy of on-demand (and breakthrough) bleeding episodes (BEs) and practically identical safety variables were recorded throughout all studies. In addition, all key laboratory parameters were measured in the same certified central laboratory by the same validated methods. FVIII concentration in patients' plasma was measured by both the one-stage and chromogenic assays. FVIII potency of FVIII concentrates used for PK and in vivo recovery investigations was measured by the central laboratory using both assays. FVIII inhibitors were assessed by the Nijmegen modification of Bethesda assay and time points for testing of inhibitory and non-inhibitory antibodies were the same in all studies. A study in previously untreated patients (GENA-05) is currently ongoing to assess the immunogenicity, efficacy and safety of Human-cl rhFVIII.

2.2. Information on the pharmaceutical formulation used in the study

Human-cl rhFVIII (Nuwiq®) is a B domain-deleted recombinant human blood coagulation factor VIII (rhFVIII) concentrate produced by Octapharma AB, Stockholm, Sweden. The protein is expressed in a human embryonic kidney (HEK) cell line derivative, HEK293F (clone 4124K), which is adapted to grow in serum-free culture medium. The product is a sulphated glycoprotein with complex-, hybrid and high mannose-type glycosylation present at the same sites as in native human plasma-derived FVIII.

Human-cl rhFVIII drug product consists of a white to off-white sterile, lyophilised powder and a solvent to prepare a solution for intravenous injection. The lyophilised 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.

3. Clinical aspects

3.1.1. Introduction

The MAH submitted a final report for pediatric GENA-13 clinical study for assessment of the long-term immunogenicity, tolerability and efficacy of *Human-cl rhFVIII* in previously treated children with severe Haemophilia A.

3.1.2. Clinical study

Study design and Study description

Objective(s)

The primary objective of this study was to determine the long-term immunogenicity and tolerability of Human-cl rhFVIII in previously treated children with severe haemophilia A. The secondary objective of this study was to determine the long-term efficacy of Human-cl rhFVIII in the prophylaxis and treatment of bleeding episodes (BEs), and in surgical prophylaxis in previously treated children with severe haemophilia A.

Study design

This was a prospective, open-label, uncontrolled, international, multicenter phase 3b study designed to collect long-term data on the immunogenicity, tolerability, and efficacy of Human-cl rhFVIII. Participation in GENA-13 was open to all evaluable patients who had completed study GENA-03 with a study participation period of 6 months. The screening visit for GENA-13 coincided with the study completion visit of GENA-03, with results transferred between databases.

Study population /Sample size

Eligible subjects have completed GENA-03 study with a study participation of 6 months and provided that prophylaxis with Human-cl rhFVIII continued without intermediate interruption. Eligible subjects further have the capability to understand and comply with the relevant aspects of the study and have voluntary informed written and signed consent obtained from the parents (or legal guardians).

Patients who developed FVIII inhibitors (≥ 0.6 Bethesda units [BU]) in the course of study GENA-03 or have any severe liver or kidney disease (alanine aminotransferase and aspartate aminotransferase levels >5 times of upper limit of normal, creatinine >120 µmol/L) were not eligible for the study.

In total, 56 patients have completed GENA-03 study from which 49 were enrolled into GENA-13 study.

Treatments

For prophylactic treatment, a dose of 30–40 IU FVIII/kg BW was selected in an every-other-day or a 3-times-a-week dosage regimen. Two dose escalations of approximately +5 IU FVIII/kg BW each were recommended if two or more spontaneous bleeding episodes (BEs) within one month were reported.

Dosage recommendations for the treatment of BEs depended on the location and extent of bleeding as well as on the clinical situation of the patient. Minor haemorrhages were treated with 20–30 IU FVIII/kg BW. 30–40 IU FVIII/kg BW were used to treat moderate to major haemorrhages. Treatment

was repeated every 12–24 hours until BE had resolved. Major to life-threatening haemorrhages were initially treated with a dose of 50–60 IU FVIII/kg BW and repeated doses of 20–25 IU FVIII/kg BW every 8–12 hours were administered until BE had resolved.

For prophylaxis treatment in minor surgeries, 25–30 IU FVIII/kg BW were administered within 3 hours before surgery to achieve an intended target peak level of about 50–60%. Dosage was repeated every 12–24 hours until healing was complete. In major surgeries, prophylactic doses of 50 IU FVIII/kg BW within 3 hours before surgery were administered to achieve an intended target peak level of approximately 100%. Treatment was repeated if necessary after 6–12 hours initially and for at least 6 days until healing is complete.

Outcomes/endpoints

Primary endpoints:

- Long-term immunogenicity, assessed based on inhibitor activity determined using the modified Bethesda assay (Nijmegen modification) and anti-rhFVIII antibody measurements.
- Long-term tolerability, assessed by monitoring adverse events (AEs), vital signs, laboratory parameters (hematology and clinical chemistry) and physical examination (including Hemophilia Joint Health Score HJHS) throughout the study duration.

Secondary endpoints:

- Long-term efficacy of prophylactic treatment, assessed based on the monthly and annual rates (ABR) of spontaneous and total BEs.
- Long-term efficacy in the treatment of BEs, assessed by the patient/patient's parents or legal guardians at the end of a BE.
- Efficacy in surgical prophylaxis, assessed by the surgeon at the end of surgery and postoperatively by both the surgeon and the haematologist.

Statistical Methods

The statistical analysis of all endpoints was performed descriptively and exploratory as appropriate. For analysis, a safety population (i.e. all patients who received at least one dose of Human-cl rhFVIII), an efficacy population (Intention-to-treat, Intention-to-treat Bleeding, and Intention-to-treat Surgery) and specific subgroups (patients aged 2–5 years or 6–12 years at the time of enrolment into GENA-03) were defined.

Results

Recruitment/ Number analysed

49 from 56 patients who have completed GENA-03 study were enrolled into GENA-13 study. All 49 patients are included in the analysis.

Baseline data

All patients had severe haemophilia A and were white and of neither Hispanic nor Latino ethnicity. Genetic defects were documented in 47 of the 49 enrolled patients. Median age of the entire patient population was 6 (range, 3–13) years. Age distribution at the time of enrolment was at follows: 2-5 years = 26 patients and 6-12 years = 23 patients. The mean duration of participation in the study (= treatment duration) was 29.4 ± 6.9 months (median: 30.1 months, range, 9.6–53.2). Slightly more than one third of the patients had a family history of haemophilia (N=19, 38.8%), and 3 patients (6.1%) had a family history of inhibitors.

Efficacy results

Prophylactic treatment:

Median duration of prophylactic treatment was 30 months (range, 9.5–52) and the median dose per prophylactic infusion was 36.5 IU/kg (range, 28.5–61). 27 out of the 49 enrolled patients experienced 81 spontaneous BEs during the study course resulting in an efficacy rating of "excellent" (i.e. BE monthly rate < 0.75) for all patients. The ABR for spontaneous BEs in the 49 patients was 0.67. The sponsor stated that continued prophylactic treatment with Human-cl rhFVIII in GENA-13 study significantly decreased ABR for spontaneous BEs in the younger age group (2 – 5 years) when compared to GENA-3 study (ABR 1.67), in which all patients were treated prophylactically using a recommended dosage regimen of 30–40 IU FVIII/kg BW every other day or 3 times weekly. 35 out of the 49 patients (71%) did not have a single abnormal joint score and an improvement of the HJHS from 0.69 ± 2.99 (range, 0–20) to 0.23 ± 0.84 (range, 0–4) and the global gait score from 0.15 ± 0.65 (range, 0–4) to 0.06 ± 0.25 (range, 0–1) could be observed until study end.

Treatment of BEs:

41 patients had 336 BEs (spontaneous 24%, traumatic 62%, other/undocumented cause 16%) from which were 54.2% minor bleedings, 43.4% moderate to major, 1.5% major to life threatening and 0.9% of undocumented severity. About one third of the BEs was located to joints. 331 BEs required treatment of which 71.4% were treated with one infusion, 13.5% with two infusions and 3-8 infusions were administered to 15.1%. Median dose per infusion was 39.8 IU/kg (range, 24.6–111.1), and the median dose per BE was 47.4 IU/kg (range, 24.6–351.3). Efficacy was rated "excellent" for 57.2% of the 311 treatment requiring BEs , "good" for 24.1%, "moderate" for 14.8%, "none" for 1.9% (these were of moderate to major severity and were treated with 4-8 infusions) and for 1.9% treatment efficacy was undocumented. Overall, in GENA-13 study 81.4% treated BEs had an efficacy rating of either "excellent" or "good" which is comparable to the results of the GENA-03 study (82.4%).

Surgical prophylaxis:

16 out of the 49 patients underwent 27 surgical procedures of which 24 were treated with Human-cl rhFVIII. 12 of 24 were major surgery procedures and included removal of port-a-cath, vascuport exchange, dental extraction, ureter reimplanation, ingrown toe nail and evacuation of haemarthrosis of knee with splint installation. Median doses per infusion were 49.6 and 41.5 IU/kg, respectively, for

major (n = 12) and minor surgeries (n = 12). The median number of infusions for minor and major surgeries was 8 (range, 2–19) and 11 (range, 3–37), respectively. Efficacy assessment of surgical prophylaxis with Human-cl rhFVIII was available for 21 surgical procedures and all them rated "excellent" (intraoperative assessment by the surgeon and the overall assessments by the surgeon and the haematologist were available for 16 surgeries, 5 surgeries had at least one assessment and 3 surgeries had no efficacy assessment).

Safety results

The safety population comprised 49 patients with a median number of exposure days (EDs) of 424 (range, 145–802) and a median number of infusions of 424 (range, 145–823). Patients received a total of 20,518 infusions (prophylaxis, n=19,725; treatment of BEs, n=485; surgical prophylaxis, n=261; in vivo recovery, n=47).

45 patients had a total of 317 adverse events (AEs) of which 81% were mild, 17% moderate and 8% severe. Respiratory tract infections, headache, pyrexia and chills were amongst the most common AEs. On case of mild dyspnea was considered to be drug-related. No AE resulted in withdrawal of the patient from the study.

30 serious AEs (SAEs) occurred in 21 patients, one of them was considered drug-related (mild pyrexia). 13 out of 30 SAEs were related with the patients' underlying condition (i.e. device-related events, hematuria, hematoma, hemarthrosis and synoviorthesis).

In total, two probably or possibly drug-related ADRs occurred, i.e. mild pyrexia and mild, temporary dyspnea.

Pyrexia was experienced in one patient after rhFVIII infusion (331 EDs) and lasted for about 1 day. 11 days before the patient had already been hospitalised with fever and shivering and a diagnosis of porth-a-cath infection. He recovered and had been discharged from hospital after 5 days. 6 days later he was again hospitalised due to fever. Laboratory test were performed including blood culture, blood morphology and CRP. No results on these analyses have been provided by the sponsor. The patient was treated with amikacin, paracetamol, and ibuprofen and discharged from hospital after 3 days. The event was classified as SAE because hospitalisation was required and as possibly drug-related. The same patient was again hospitalised with symptoms of fever above 3 month later which was considered not drug-related. Central catheter of this patient was changed again 3 month later due to application site erosion (not related).

Mild dyspnea was experienced after 134 EDs by one patient and lasted for about 3 minutes, after which the patient recovered. This AE was classified as probably or possibly related to treatment with Human-cl rhFVIII. The sponsor further notes, that other non-drug-related AEs in this patient included house dust allergy which was diagnosed few days after AE occurrence.

In the 49 patients, incidence of FVIII inhibitors was 0%. One patient developed low titers of non-inhibitory anti-rhFVIII antibodies during the study; prophylactic efficacy in this patient was rated "excellent". As stated by the sponsor, no cases of thromboembolism or hypersensitivity were observed and results of physical examination and vital sign monitoring did not indicate any treatment related safety concerns.

3.1.3. Discussion on clinical aspects

In accordance with Article 46 of Regulation (EC) No. 1901/2006, the MAH submitted the final study report of GENA-13 clinical trial (eCTD 0041 and 0042) investigating the long-term immunogenicity, tolerability and efficacy of Human-cl rhFVIII (Nuwiq®) in 49 previously treated pediatric patients with severe haemophilia A. Hemostatic efficacy could be demonstrated for the majority of patients receiving Human-cl rhFVIII for on-demand treatment as well as for treatment for long-term and surgical prophylaxis. However, in accordance with the guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products (EMA/CHMP/BPWP/144533/2009 rev. 1), sufficient data on FVIII consumption for prophylaxis and on-demand therapy should be provided. Additionally, the substantial numbers of BEs which could not be treated sufficiently requires further explanation by the MAH.

With regard to safety aspects, Human-cl rhFVIII was administered for prophylactic and on-demand treatment with a sufficient number of EDs. 2 out of 317 reported AEs were considered possibly drug-related, i.e. one case of mild pyrexia and one case of mild, temporary dyspnea. Indeed, pyrexia and dyspnea potentially are indicative of drug-mediated hypersensitivity reactions that may have manifested in these 2 patients. However, pyrexia in one patient appears to be more likely associated with recurrent infection of a port-a-cath implantable venous access system and the patient who experienced temporary and mild dyspnea after 134 EDs received approximately 150 EDs during the following year without recurrence of this AE. Thus, both AEs are not considered to indicate hypersensitivity reactions related to Human-cl rhFVIII. In terms of FVIII antibodies, one patient developed confirmed low-titers of non-inhibitory anti-rhFVIII antibodies which does not raise significant concerns. No cases of thromboembolism or hypersensitivity were detected. No further safety issues have been identified in pediatric patients from this trial.

4. Rapporteur's overall conclusion and recommendation

In summary, the data reported from the GENA-13 study are not expected to change the current benefit-risk profile. However, presentation of efficacy and safety data is not sufficient and the MAH is requested to provide further data from GENA-13 study to accurately reflect current status of pediatric assessment (see section 5 "Additional clarification requested").

☒ **Not fulfilled:**

5. Additional clarification requested

Based on the data submitted, the MAH should address the following questions as part of this procedure:

List of Questions:

1. The MAH is asked to provide a line listing of all the studies included in the development program (nonclinical and clinical). Provided information should include at least study title, study number, date of completion, and date of submission of final study report.

2. According to applicable guideline (EMA/CHMP/BPWP/144533/2009 rev.1), data on FVIII consumption for prophylaxis as well as for on-demand treatment (dose/kg) should be provided. With regard to efficacy results of prophylactic treatment regime and of surgical prophylaxis, such data are missing. Thus, the MAH is asked to provide data on monthly or annual FVIII consumption (IU/kg) as well as consumption related to major surgical procedures. E.g. age-related subgroup analysis should be provided and compared with adults (age-groups: 2-6, 6-12, 12-18 and >18 years). Regarding FVIII consumption in on-demand treatment, dose per infusion and per BE were provided, however, the median doses per bleeding episode exhibited a large variation with a range of 24.6–351.3 IU/kg. The MAH is requested to explain this wide range.

3. As outlined by the MAH, a number of patients were excluded from the efficacy analysis due to overdosing of more than 40% (Patient IDs: 13-01-04, 13-01-05, 13-01-07, 13-43-03). The MAH is asked to provide further details of these subjects. In particular, the MAH needs to justify whether the current dose recommendation in the SmPC is adequate.

4. In the treatment of BEs, a substantial number of efficacy ratings were "moderate" or "none" in both pediatric studies, GENA-03 (17.6%) and GENA-13 (16,7%). Though some details are provided about none responding subjects from GENA-13, the MAH should display and reflect data of all subjects that have not been treated successfully.

The timetable is a 30 day response timetable <u>with</u> clock stop.

6. MAH responses to Request for supplementary information

The MAH has submitted responses with eCTD 050 according to the request for supplementary information on 18 April 2017.

Question 1

The MAH is asked to provide a line listing of all the studies included in the development program (nonclinical and clinical). Provided information should include at least study title, study number, date of completion, and date of submission of final study report.

MAH's responses

Non clinical studies

Product Name: Nuwiq Active substance: simoctocog alfa

Study title	**Study number**	**Date of completion**	**Date of submission of final study report**
Recombinant Human Factor VIII (rhFVIII): Single Dose Toxicity Study by Intravenous Injection to CD Rats	DWL 0003/063496	21-Sept-2006	29-May-2013
Cross-over Comparative Study of the Efficacy and Pharmacokinetics of a novel B Domain deleted Recombinant Coagulation Factor VIII Concentrate in a Canine Model of Hemophilia A	- (internally referred to as "Oct 10 2007")	10-Oct-2007	29-May-2013
Recombinant Human Factor VIII (rhFVIII): Local Tolerance Study in the Rabbit following Perivenous injection	DWL 0004/073723	19-Feb-2008	29-May-2013
Recombinant Human Factor VIII (rhFVIII): Toxicity Study by Intravenous Injection to Cynomolgus Monkeys for 4 weeks followed by a 2 week recovery period	DWL 0002/064067	23-May-2008	29-May-2013
Recombinant Human Factor VIII (rhFVIII): Preliminary Toxicity Study by Intravenous Bolus Injection to Cynomolgus Monkeys	DWL 0001/063743	27-May-2008	29-May-2013
EpiScreen™ T Cell Epitope Mapping of Factor VIII Linker Sequences	OCT01	11-Mar-2010	29-May-2013
EpiScreen™ Study 2 Immunogenicity Testing VWF Pre-Screen Study	Pre-screen: OCT01 Study 2	22-Nov-2010	29-May-2013
Pharmacokinetics of Human-cl rhFVIII in Hemophilia Dogs	OC11-0200	08-Jul-2011	29-May-2013

EpiScreen™ Study 2 Immunogenicity Testing of Vivante Isoforms with von Willebrand Factor	OCT02 Study 4	17-Nov-2011	29-May-2013
EpiScreen™ Study 2 Immunogenicity Testing of Factor VIII Products with von Willebrand Factor	OCT01 Study 2	16-Nov-2012	29-May-2013
Local Tolerance Study of Four Nuwiq® Strengths following a single perivenous Administration in Rabbits	LPT 33166	18-Apr-2016	not yet submitted

Clinical studies

Product Name: Nuwiq Active substance: simoctocog alfa

Study title	**Study number**	**EudraCT No.**	**Date of completion (i.e. date of final study report)**	**Date of submission of final study report**
Clinical Study to Investigate the Pharmacokinetics, Efficacy, Safety and Immunogenicity of Human-cl rhFVIII, a Newly Developed Human Cell-Line Derived Recombinant FVIII Concentrate in Previously Treated Patients with Severe Haemophilia A	GENA-01[1]	2008-001563-11	15-Feb-2013	29-May-2013
Clinical Study to Investigate the Long-Term Efficacy, Safety, and Immunogenicity of Human-cl rhFVIII in Previously Treated Patients with Severe Haemophilia A – Extension Study to GENA-01	GENA-11	2010-023242-69	16-Jul-2013	17-Jan-2014
Clinical Study To Investigate the Efficacy, Safety, And Immunogenicity of Human-cl rhFVIII in Previously Treated Patients with Severe Haemophilia A	GENA-08[1]	2009-011055-43	19-Jul-2012	29-May-2013
Prospective Clinical Study in Children with Severe Haemophilia A to Investigate Clinical Efficacy, Immunogenicity, Pharmacokinetics, and Safety of Human-cl rhFVIII	GENA-03[1]	2010-018644-14	15-Feb-2013	29-May-2013
Clinical Study in Previously Treated Children with Severe Haemophilia A to Investigate the Long-Term	GENA-13	2011-001785-	22-Nov-2016	07-Dec-2016

Immunogenicity, Tolerability and Efficacy of Human-cl rhFVIII		17		
Clinical Study to Investigate the Pharmacokinetics, Efficacy, Safety and Immunogenicity of Human-cl rhFVIII in Previously Treated Patients with Severe Haemophilia A	GENA-09[2]	2008-006172-29	14-Dec-2010	29-May-2013
Clinical Study to Investigate the Long-Term Safety and Efficacy of Human-cl rhFVIII in Previously Treated Patients with Severe Haemophilia A	GENA-04[2]	2009-014422-41	22-Mar-2012	29-May-2013
Immunogenicity, Efficacy and Safety of Treatment with Human-cl rhFVIII in Previously Untreated Patients with Severe Haemophilia A	GENA-05	2012-002554-23	Ongoing	Not applicable
Extension Study for Patients who Completed GENA-05 (NuProtect) – to Investigate Immunogenicity, Efficacy and Safety of Treatment with Human-cl rhFVIII	GENA-15	2013-003997-28	Ongoing	Not applicable
Prospective, Multinational, Non-interventional Post-Authorisation Study to Document the Long-Term Immunogenicity, Safety, and Efficacy of Human-cl rhFVIII (simoctocog alfa) in Patients with Haemophilia A treated in Routine Clinical Practice	GENA-99	Not applicable	Ongoing	Not applicable
Prospective, Open-Label, Multicentre Phase 3b Study to Assess the Efficacy and Safety of Individually Tailored Prophylaxis with Human-cl rhFVIII in Previously Treated Adult Patients with Severe Haemophilia A	GENA-21	2013-001556-35	13-Jan-2016	not yet submitted
Prospective, Open-Label, Multicentre Phase 3b Study to Assess the Efficacy and Safety of Personalized Prophylaxis with Human-cl rhFVIII in Previously Treated Adult Patients with Severe Haemophilia A	GENA-21b	2014-002986-30	Ongoing	Not applicable

[1], pivotal study for obtaining marketing authorization

[2], supportive study for obtaining marketing authorization

Assessment of the MAH's responses

The MAH provided adequate line listings of nonclinical as well as clinical studies included in the development program.

Conclusion

The question has been answered satisfactorily.

Question 2

According to applicable guideline (EMA/CHMP/BPWP/144533/2009 rev.1), data on FVIII consumption for prophylaxis as well as for on-demand treatment (dose/kg) should be provided. With regard to efficacy results of prophylactic treatment regime and of surgical prophylaxis, such data are missing. Thus, the MAH is asked to provide data on monthly or annual FVIII consumption (IU/kg) as well as consumption related to major surgical procedures. E.g. age-related subgroup analysis should be provided and compared with adults (age-groups: 2-6, 6-12, 12-18 and >18 years). Regarding FVIII consumption in on-demand treatment, dose per infusion and per BE were provided, however, the median doses per bleeding episode exhibited a large variation with a range of 24.6–351.3 IU/kg. The MAH is requested to explain this wide range.

MAH's responses

FVIII consumption for prophylaxis

Data on FVIII consumption for prophylaxis per month for the entire population were provided in the Study Report, section 11.4.1, Table 17. Corresponding data for the age groups 2-5 years and 6-12 years were provided in the Table 14.2.3.1-1.

Table 1 summarizes the FVIII monthly consumption for prophylaxis by age group in comparison to data obtained from pivotal studies in children (GENA-03) and adults (GENA-08) submitted for obtaining marketing authorization.

Table 1: FVIII consumption per month for prophylaxis in GENA-13 and pivotal studies.

Study No.	Age group (years)	No. of patients	FVIII consumption per month (IU/kg/) median (range)	FVIII consumption per month (IU/kg/) mean ± SD
GENA-13	2-12	49	519.0 (368.4-791.8)	531.2 ± 100.8
GENA-13	2-5	26	559.9 (373.1-791.8)	557.3 ± 98.2
GENA-13	6-12	23	488.3 (368.4-774.0)	501.7 ± 97.4
GENA-03[1]	2-12	59	521.9 (332.3-888.5)	527.7 ± 112.3
GENA-03[1]	2-5	29	513.4 (359.0-888.5)	525.0 ± 120.4
GENA-03[1]	6-12	30	533.8 (332.3-809.5)	530.4 ± 105.9
GENA-08[1]	≥18	32	468.7 (208.4-582.6)	466.1 ± 65.5

[1], pivotal study for obtaining marketing authorization
Source: GENA-13: Table 14.2.3.1-1; GENA-03: Table 14.2.14.2, Table EMA_Q143.3.1, Table EMA_Q143.3.2 *(related to responses to initial MAA D120 LoQ)*; GENA-08: Study Report, Table 11

In general, FVIII consumption for prophylaxis in the paediatric study GENA-13 and its predecessor study GENA-03 were similar to each other and was higher than in adults.

Data on FVIII consumption for prophylaxis by treatment regime in GENA-13 were provided in Table 14.2.3.1-3 and are summarized in Table 2.

Table 2: FVIII consumption per month for prophylaxis in GENA-13 by prophylactic treatment regime and age group.

Age group (years)	Treatment regimen	No. of patients[1]	FVIII consumption per month (IU/kg/) median (range)	FVIII consumption per month (IU/kg/) mean ± SD
2-5	Every other day	n = 13	626.5 (433.4-791.8)	606.3 ± 97.7
2-5	3 times per week	n = 13	546.3 (373.1-588.5)	508.2 ± 72.9
6-12	Every other day	n = 10	546.5 (441.6-774.0)	569.7 ± 104.9
6-12	3 times per week	n = 8	439.8 (368.4-488.3)	430.6 ± 39.2

[1], Five patients could not be assigned to either treatment regimen
Source: GENA-13: Table 14.2.3.1-3

In general, younger children used more FVIII than older children and every other day prophylaxis required more FVIII than prophylaxis given three times per week.

FVIII consumption for major surgery

Data on FVIII consumption for surgical prophylaxis (in total, for minor and for major surgery) were provided in Table 14.2.5.2-3. Data on FVIII consumption for major surgeries are summarized in Table 3 in comparison to data obtained from pivotal studies submitted for obtaining marketing authorization.

Table 3: FVIII consumption for major surgeries in GENA-13 and pivotal studies by age group.

Study No.	Age (years)[1]	No. of major surgeries treated with Nuwiq	Number of infusions (median, range)	Dose for surgical prophylaxis (IU/kg), median, range
GENA-13	2-12	12	6 (3-24)	564.7 (130.0-166.7)
GENA-13	2-5	5	8 (7-29)	429.1 (288.5-1019.2)
GENA-13	6-12	7	13 (3-37)	604.7 (130.0-1666.7)
GENA-03[2]	2-12	5	5 (3-20)	183.3 (150.0-593.2)
GENA-03[2]	2-5	2	12 (4-20)	381.6 (170.0-593.2)
GENA-03[2]	6-12	3	5 (3-5)	183.3 (150.0-233.3)
GENA-01[2]	12-65	1	15	746.9
GENA-08[2]	18-75	4	12.5 (5-25)	400.7 (183.3-1028.7)

[1], the age range is for the entire population, not necessarily for those who had major surgeries
[2], pivotal study for obtaining marketing authorization
[3], the patent who underwent major surgery was 49 years old
Source: GENA-13: Table 14.2.5.2-3, Table 14.2.5.1-4; GENA-03: Table 14.2.36, Table 14.2.39, Table 14.2.40, Table_EMA_1.1, Table _EMA_1.2, Table _EMA_2.1, Table _EMA_2.2; GENA-01: Study report section 11.4.3.4, Table 24; GENA-08: Table 14.2.24.2, Study Report section 11.4.2.3, Table 17

In general, the total consumption of FVIII for prophylaxis in major surgeries seem to be dependent on the number of infusions.

FVIII consumption for on-demand treatment of bleeding episodes

Data on FVIII consumption for on-demand treatment per month and per year were provided in Table 14.2.4.3-1. Table 4 summarizes the monthly FVIII consumption for on demand treatment by age group in comparison to data obtained from pivotal studies submitted for obtaining marketing authorization.

Table 4: FVIII consumption per month for treatment of bleeding episodes in GENA-13 and pivotal studies.

Study number	Age range (years)	No. of patients with treated bleeding episodes	FVIII consumption per month (IU/kg/) median (range)	FVIII consumption per month (IU/kg/) mean ± SD
GENA-13	2-12	40	9.0 (1.0-191.1)	18.0 ± 32.0
GENA-13	2-5	20	6.0 (1.0-24.8)	8.3 ± 7.3
GENA-13	6-12	20	14.4 (1.0-191.1)	27.7 ± 43.0
GENA-03[1]	2-12	32	25.9 (3.9-409.4)	54.4 ± 83.4
GENA-03[1]	2-5	12	34.4 (4.1-241.4)	48.1 ± 64.4
GENA-03[1]	6-12	20	22.1 (3.9-409.4)	58.1 ± 94.4
GENA-01[1]	12-65[2]	22	153.5 (24.4-410.3)	156.9 ± 79.0
GENA-08[1]	18-75	15	10.1 (3.1-57.2)	17.7 ± 16.4

[1], pivotal study for obtaining marketing authorization
[2], two of the 22 GENA-01 patients were between 12 and 17 years.
Source: GENA-13: Table 14.2.4.3-1; GENA-03: 14.2.30, Table _EMA_3.1, Table _EMA_3.2; GENA-08: Table 14.2.19; GENA-01: Table 14.2.34

The FVIII consumption for treatment of bleeding episodes in the extension study GENA-13 was lower than in the predecessor study GENA-03 (and very similar to that for adult patients treated prophylactically) suggesting a potential benefit of long-term prophylactic treatment.

Doses per bleeding episode

The median doses per bleeding episode vary widely in GENA-13 (24.6-351.3 IU/kg), but a similar variability was also observed in the previous studies with Nuwiq, both in children (25-1521 IU/kg) and in the adults (8-657 IU/kg), see Table 5. The wide range is probably due to the varying number of infusions used to treat a bleeding episode. Although the majority of BEs were treated with one or two infusions of Nuwiq (91.4%/5.8% in GENA-01, 81.5%/7.4% in GENA-08, 68.6%/12.7% in GENA-03, 71.4%/135.5% in GENA-13), some bleeds needed more and in one case in GENA-03 even with 22 infusions. Overall, both the doses per bleeding episodes and the number of infusions used to treat a bleeding episode in GENA-13 study are very similar to those of the predecessor study GENA-03.

Table 5: FVIII consumption for treatment of bleeding episodes in GENA-13 and pivotal studies.

Study number	Age group (years)	No. of BEs treated with Nuwiq	Infusions per BE median (range)	Dose per BE (IU/kg) median (range)
GENA-13	2-12	311	1 (1-8)	47.4 (24.6-351.3)
GENA-13	2-5	71	1 (1-8)	40.8 (25.3-324.3)
GENA-13	6-12	240	1 (1-8)	48.8 (24.6-351.3)
GENA-03[1]	2-12	108	1 (1-22)	43.9 (25-1521)
GENA-03	2-5	33	1 (1-22)	52.6 (30-1521)
GENA-03	6-12	75	1 (1-15)	43.9 (25-600)
GENA-01[1]	12-65[2]	986	1 (1-13)	30.9 (8-657)
GENA-08[1]	18-75	30	1 (1-12)	33.3 (20-353)

[1], pivotal study for obtaining marketing authorization
[2], two of the 22 GENA-01 patients were between 12 and 17 years old
Source: GENA-13: Table 14.2.4.1-3; Table 14.2.4.3-5, Table 14.4.3-9, Ergomed Table 20 March 2017; GENA-03: Study report, section 11.4.2.3, Table 32, Table EMA_Q142.3.1, Table EMA_Q142.3.2 *(related to responses to initial MAA D120 LoQ)*; Table _EMA_4.1, Table _EMA_4.2; GENA-01: Study Report, Table 22; GENA-08; Study Report, Table 15

Assessment of the MAH's responses

The MAH provided sufficient data analysis of FVIII consumption for prophylaxis and on-demand treatment as well as for major surgery in comparison to pivotal studies. Furthermore, the variation of FVIII doses used for on-demand treatment of bleeding episodes was comparable to other studies with Nuwiq. Thus, no regulatory consequences are required.

Conclusion

This issue has been solved.

Question 3

As outlined by the MAH, a number of patients were excluded from the efficacy analysis due to overdosing of more than 40% (Patient IDs: 13-01-04, 13-01-05, 13-01-07, 13-43-03). The MAH is asked to provide further details of these subjects. In particular, the MAH needs to justify whether the current dose recommendation in the SmPC is adequate.

MAH's responses

We would like to clarify that patients 13-01-04, 13-01-05, 13-41-07 (not 13-01-07 as mentioned in comment 3), and 13-43-03 were excluded from the Per Protocol (PP) population because of overdosing. During the data review meeting it was decided to exclude these 4 patients from the PP population because of deviations from the recommended prophylactic dose: overdosing (i.e., a deviation of at least +20% from the highest recommended dose) in more than 40% of prophylactic infusions. Thus, these patients were considered major protocol violators because of treatment deviations (as well as 3 other patients due to noncompliance with completing the study diary), see Clinical Study Report, section 10.3.1.

We would like to further clarify that efficacy analysis (i.e. calculation of the annualized bleeding rate as well as FVIII consumption for prophylaxis) was also performed for these 4 patients as they are

included in the ITT population analysis. Table 6 below provides some details on these 4 patients in comparison to the ITT and PP population.

Table 6: FVIII consumption for prophylaxis and annualized bleeding rate.

Analysis population	FVIII dose per prophylactic infusion (IU/kg)	FVIII consumption per month (IU/kg) mean ± SD	Annualized total bleeding rate
ITT (n= 49)	38.6 ± 6.7	531.2 ± 100.8	2.91 ± 4.66
PP (n =42)	37.5 ± 5.4	517.2 ± 88.5	3.12 ± 4.90
Patients excluded because of "overdose"			
13-01-04	61.0	773.8	0.3
13-01-05	48.8	629.9	0.6
13-41-07	47.4	625.3	1.4
13-43-03	51.4	765.0	0.0

Date are mean ± SD for ITT and PP; individual (mean) data for 4 patients excluded from PP because of overdose
Source: GENA-13: Table 14.2.3.1-1, Table 14.2.3.1-2, Table 14.2.3.2-3, Table 14.2.3.2-1, Listing 16.2.6.2-1, Listing 16.2.6.3-1

Patient #13-01-04, 4 years, 21.9 kg, had 476 prophylactic infusions, 422 (88.7%) of them were overdosed. The highest prophylactic dose administered was 123.97 IU/kg, with overdoses reported to have been due to parent initiative. In GENA-03, the mean prophylactic dose per injection and per month was 50.1 IU/kg and 888.5 IU/kg (and thus 12.9% lower than in GENA-03), respectively.

Patient #13-01-05, 6 years, 28.3 kg, had 484 prophylactic infusions, 299 (61.8%) of them were overdosed. The highest prophylactic dose administered was 98.36 IU/kg, with no reasons for overdosing given. In GENA-03, the mean prophylactic dose per injection and per month was 38.1 IU/kg and 571.1 IU/kg (and thus 10.3% higher than in GENA-03), respectively.

Patient #13-41-07, 4 years, 19.8 kg, had 449 prophylactic infusions, 246 (54.8%) of them were overdosed. The overall prophylactic dose was consistently 1000 IU per infusion, resulting in doses between 50.5 IU/kg at the beginning (BW: 19.8 kg) and 42.7 IU/kg at the end of the patient's study participation (BW: 23.8 kg). In GENA-03, the mean prophylactic dose per injection and per month was 35.0 IU/kg and 464.0 IU/kg (and thus 34.8% higher than in GENA-03), respectively.

Patient #13-43-03, 6 years, 18.4 kg, had 378 prophylactic infusions, 316 (83.6%) of them were overdosed. The overall prophylactic dose was consistently 1000 IU per infusion, resulting in doses between 54.35 IU/kg at the beginning (BW: 18.4 kg) and 46.73 IU/kg at the end of the patient's study participation (BW: 21.6 kg). In GENA-03, the mean prophylactic dose per injection and per month was 56.7 IU/kg and 809.5 IU/kg (and thus 5.5% lower than in GENA-03), respectively. Source: GENA-13: Table 2.2-4 02-Sep-2016 GASD for Octapharma.

Overall, the prophylactic dosing in GENA-13 for the entire study population was very similar to those on GENA-03, which served as the pivotal paediatric study for approval of Nuwiq. To a somewhat lesser degree this is also true for the four patients with overdosing in GENA-13. In conclusion, we find that the current dose recommendation in the SmPC for children "The posology is the same in adults and children, however, shorter dose intervals or higher doses may be necessary for children" is still adequate.

Assessment of the MAH's responses

The MAH has sufficiently addressed the question and provided further data on the four overdosed patients. With reference to these and the overall data of paediatric GENA-13 study, no regulatory actions must be taken.

Conclusion

This point has been solved.

Question 4

In the treatment of BEs, a substantial number of efficacy ratings were "moderate" or "none" in both pediatric studies, GENA-03 (17.6%) and GENA-13 (16,7%). Though some details are provided about none responding subjects from GENA-13, the MAH should display and reflect data of all subjects that have not been treated successfully.

MAH's responses

Efficacy of treatment of a bleeding episode was rated as "moderate" in 46 (14.8% of all bleeding episodes) cases in 15 patients and as "none" in 6 (1.9%) cases in 4 patients. More information on these cases is summarised in Additional Listings 2 (for "none" assessments) and Additional Listings 1 (for all "moderate" assessments), both derived from Listing 16.2.6.3-3 – Part 2. For example, all treatments assessed as "none" related to moderate to major bleeding episodes which required at least 4 infusions. Thus, as it was also the case for "moderate" assessments, the efficacy rating was in line with the criteria provided in the protocol ("requiring more than 2 infusions"). Additional Listing 3 indicates the efficacy assessment of all bleeding episodes in patients who had at least one bleeding episode treatment assessed as "moderate" or "none". In most cases the other BEs were treated successfully.

One reason of the lower percentage of successfully treated bleeding episodes in children as compared to the on-demand study in adults might be that proportion of traumatic bleeding episodes was higher in children than in adults (Table 7).

Table 7: Efficacy of treating bleeding episodes and type of bleeding in GENA-13 and pivotal studies

Study number	Age range (years)	No. of BEs treated with Nuwiq	BEs treated successfully (%)	Traumatic BEs (%)
GENA-13	2-12	311	81.4%	64.0%
GENA-03[1]	2-12	108	82.4%	60.2%
GENA-01[1]	12-65	986	94.4%	34.6%
GENA-08[1]	18-75	30	100.0%	46.7%

[1], pivotal study for obtaining marketing authorization
[2], two of 22 patients were adolescents
Source: GENA-13: CSR. Table 21 and 24, Additional Listing request 2017-04-03; GENA-03: Table 34, Table 14.2.19; GENA-01: Table 14.2.22, Table 14.2.25.2; GENA-08: Table 14.2.9, Table 14.12.2

Assessment of the MAH's responses

The MAH further analysed data of unsuccessfully treated pediatric subjects from GENA-13 study showing that the number of successfully treated bleeding episodes was comparable to that of pediatric subjects from GENA-03 pivotal study. Both studies have substantially higher numbers of traumatic bleeding episodes in pediatric subjects as compared to adult subjects included in GENA-01 and -08 studies which might account for the lower percentage of successfully treated bleeds as suggested by the MAH.

Conclusion

The point has been resolved. No regulatory action required.

7. Rapporteur's overall conclusion and recommendation

In summary, the data reported from the GENA-13 study are not expected to change the favourable benefit-risk profile. It is considered that study data do not have any impact on the current EU SmPC of Human-cl rhFVIII (Nuwiq®). No regulatory action required. No additional clarification requested.

☒ **Fulfilled:**

Annex. Line listing of all the studies included in the development program

Non clinical studies

Product Name: Nuwiq Active substance: simoctocog alfa

Study title	Study number	Date of completion	Date of submission of final study report
Recombinant Human Factor VIII (rhFVIII): Single Dose Toxicity Study by Intravenous Injection to CD Rats	DWL 0003/063496	21-Sept-2006	29-May-2013
Cross-over Comparative Study of the Efficacy and Pharmacokinetics of a novel B Domain deleted Recombinant Coagulation Factor VIII Concentrate in a Canine Model of Hemophilia A	- (internally referred to as "Oct 10 2007")	10-Oct-2007	29-May-2013
Recombinant Human Factor VIII (rhFVIII): Local Tolerance Study in the Rabbit following Perivenous injection	DWL 0004/073723	19-Feb-2008	29-May-2013
Recombinant Human Factor VIII (rhFVIII): Toxicity Study by Intravenous Injection to Cynomolgus Monkeys for 4 weeks followed by a 2 week recovery period	DWL 0002/064067	23-May-2008	29-May-2013
Recombinant Human Factor VIII (rhFVIII): Preliminary Toxicity Study by Intravenous Bolus Injection to Cynomolgus Monkeys	DWL 0001/063743	27-May-2008	29-May-2013
EpiScreen™ T Cell Epitope Mapping of Factor VIII Linker Sequences	OCT01	11-Mar-2010	29-May-2013
EpiScreen™ Study 2 Immunogenicity Testing VWF Pre-Screen Study	Pre-screen: OCT01 Study 2	22-Nov-2010	29-May-2013
Pharmacokinetics of Human-cl rhFVIII in Hemophilia Dogs	OC11-0200	08-Jul-2011	29-May-2013
EpiScreen™ Study 2 Immunogenicity Testing of Vivante Isoforms with von Willebrand Factor	OCT02 Study 4	17-Nov-2011	29-May-2013
EpiScreen™ Study 2 Immunogenicity Testing of Factor VIII Products with von Willebrand Factor	OCT01 Study 2	16-Nov-2012	29-May-2013
Local Tolerance Study of Four Nuwiq® Strengths following a single perivenous	LPT 33166	18-Apr-2016	not yet submitted

Administration in Rabbits			

Clinical studies

Product Name: Nuwiq Active substance: simoctocog alfa

Study title	**Study number**	**EudraCT No.**	**Date of completion (i.e. date of final study report)**	**Date of submission of final study report**
Clinical Study to Investigate the Pharmacokinetics, Efficacy, Safety and Immunogenicity of Human-cl rhFVIII, a Newly Developed Human Cell-Line Derived Recombinant FVIII Concentrate in Previously Treated Patients with Severe Haemophilia A	GENA-01[1]	2008-001563-11	15-Feb-2013	29-May-2013
Clinical Study to Investigate the Long-Term Efficacy, Safety, and Immunogenicity of Human-cl rhFVIII in Previously Treated Patients with Severe Haemophilia A – Extension Study to GENA-01	GENA-11	2010-023242-69	16-Jul-2013	17-Jan-2014
Clinical Study To Investigate the Efficacy, Safety, And Immunogenicity of Human-cl rhFVIII in Previously Treated Patients with Severe Haemophilia A	GENA-08[1]	2009-011055-43	19-Jul-2012	29-May-2013
Prospective Clinical Study in Children with Severe Haemophilia A to Investigate Clinical Efficacy, Immunogenicity, Pharmacokinetics, and Safety of Human-cl rhFVIII	GENA-03[1]	2010-018644-14	15-Feb-2013	29-May-2013
Clinical Study in Previously Treated Children with Severe Haemophilia A to Investigate the Long-Term Immunogenicity, Tolerability and Efficacy of Human-cl rhFVIII	GENA-13	2011-001785-17	22-Nov-2016	07-Dec-2016
Clinical Study to Investigate the Pharmacokinetics, Efficacy, Safety and Immunogenicity of Human-cl rhFVIII in Previously Treated Patients with Severe Haemophilia A	GENA-09[2]	2008-006172-29	14-Dec-2010	29-May-2013

Clinical Study to Investigate the Long-Term Safety and Efficacy of Human-cl rhFVIII in Previously Treated Patients with Severe Haemophilia A	GENA-04[2]	2009-014422-41	22-Mar-2012	29-May-2013
Immunogenicity, Efficacy and Safety of Treatment with Human-cl rhFVIII in Previously Untreated Patients with Severe Haemophilia A	GENA-05	2012-002554-23	Ongoing	Not applicable
Extension Study for Patients who Completed GENA-05 (NuProtect) – to Investigate Immunogenicity, Efficacy and Safety of Treatment with Human-cl rhFVIII	GENA-15	2013-003997-28	Ongoing	Not applicable
Prospective, Multinational, Non-interventional Post-Authorisation Study to Document the Long-Term Immunogenicity, Safety, and Efficacy of Human-cl rhFVIII (simoctocog alfa) in Patients with Haemophilia A treated in Routine Clinical Practice	GENA-99	Not applicable	Ongoing	Not applicable
Prospective, Open-Label, Multicentre Phase 3b Study to Assess the Efficacy and Safety of Individually Tailored Prophylaxis with Human-cl rhFVIII in Previously Treated Adult Patients with Severe Haemophilia A	GENA-21	2013-001556-35	13-Jan-2016	not yet submitted
Prospective, Open-Label, Multicentre Phase 3b Study to Assess the Efficacy and Safety of Personalized Prophylaxis with Human-cl rhFVIII in Previously Treated Adult Patients with Severe Haemophilia A	GENA-21b	2014-002986-30	Ongoing	Not applicable

[1], pivotal study for obtaining marketing authorization

[2], supportive study for obtaining marketing authorization