EMA/CHMP/120573/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Nuwiq	simoctocog alfa
Vihuma	simoctocog alfa

Procedure No. EMEA/H/C/xxxx/WS/2156

Note

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

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Current step[1]	Description	Planned date	Actual Date	Need for discussion[2]
☐	Start of procedure	30 Aug 2021	30 Aug 2021	☐
☐	CHMP Rapporteur Assessment Report	04 Oct 2021	04 Oct 2021	☐
☐	CHMP members comments	18 Oct 2021	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	21 Oct 2021	n/a	☐
☐	Start of written procedure	26 Oct 2021	26 Oct 2021	☐
☐	RSI	28 Oct 2021	28 Oct 2021	☐
☐	Re-start of procedure	29 Nov 2021	29 Nov 2021	☐
☐	CHMP Rapporteur Assessment Report	03 Jan 2022	22 Dec 2021	☐
☐	CHMP members comments	17 Jan 2022	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	20 Jan 2022	n/a	☐
☐	Start of written procedure	25 Jan 2022	25 Jan 2022	☐
☒	Opinion	27 Jan 2022	27 Jan 2022	☐

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Octapharma AB submitted to the European Medicines Agency on 13 August 2021 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following changes were proposed:

Variation requested		Type	Annexes affected
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None

Submission of the final report from study GENA-99 and an integrated analysis report of studies GENA-99, GENA-13, GENA-15, GENA-21, GENA-21b and GENA-100.

The requested worksharing procedure proposed no amendments to the Product Information.

2. Overall conclusion and impact on the benefit/risk balance

Simoctocog alfa is a fourth-generation recombinant human factor VIII product indicated for the treatment and prophylaxis of bleeding in paediatric and adult patients with haemophilia A and co-marketed as Nuwiq and as Vihuma (MAH: Octapharma AB). For initial MA (Nuwiq: 22/07/2014), 135 patients had been enrolled in pre-authorisation clinical studies. Although relevant information on general safety aspects were available and efficacy (restoration of factor VIII levels and stopping or prevention of bleeding) was demonstrated, data were insufficient to estimate all clinical aspects of therapy, in particular immunogenicity. In order to meet the post-authorisation requirements of the FVIII Guideline (EMA/CHMP/BPWP/144533/2009), the MAH has now submitted the final report from study GENA-99, a prospective, multinational, non-interventional post-authorisation study to document the long-term immunogenicity, safety, and efficacy of simoctocog alfa in patients with haemophilia A treated in routine clinical practice. The goal of this study was to collect data in 200 PTPs, however, it was completed in 2021 with data obtained from 78 patients. In agreement with EMA the MAH had proposed that other post-authorisation studies could be in support to meet regulatory standards. Therefore, an integrated analysis report of interventional studies GENA-13, GENA-15, GENA-21, GENA-21b and non-interventional studies GENA-99 and GENA-100 has also been submitted. No amendments of the product information are proposed.

As noted, only 78 HA patients (68 with severe HA) were treated almost exclusively prophylactically with Nuwiq in GENA-99 study. 61 patients in GENA-99 had ≥100 exposure days (EDs) and FVIII consumption was in line with the SmPC. Mean annualized bleeding rate (ABR) for all bleeds was 4.09 (SD 6.47, median 2.39 with IQR 0-4.87 and full range of 0-38.7) and consistent with the ABR in the 6 months prior to the study: median of 2.0 (IQR: 0-6, full range 0-36, mean 4.3, SD 6.82). On-demand treatment success was 88.2% and evaluated from 246 bleeding episodes (BE) in 48 prophylactically treated patients. A mean of 1.78 (SD 2.02) infusions (median 1.0, IQR: 1.00, 2.00; range: 1-24) was required for bleeding control with a median dose of 35.65 IU/kg per infusion per BE (IQR: 27.78, 42.64; range: 14.0-76.1). This is in line with data from the pivotal studies. Three patients each had one bleeding episode for which treatment efficacy was assessed as none. Individual reasons for the none-effective ratings (one BE was sub-optimally treated and two cases were target joint bleeds) are

acknowledged and additional data indicated that these patients generally responded to Nuwiq treatment.

In the GENA-pool analysis, 216 HA patients (208 with severe HA), prophylactically treated with Nuwiq for ≥100 EDs, have been evaluated for efficacy (prophylactic efficacy, on-demand treatment of breakthrough bleeds, surgical prophylaxis) and safety to meet the requirements of the EMA FVIII Guideline. Patient characteristics were balanced among age, body weight, race/ethnicity, and geographical location of study sites. Treatment success rates for BEs occurring under prophylactic treatment were 92.1% for minor, 78.7% for moderate to major, and 57.5% for major to life-threatening bleeds (overall treatment success was 84.3%). These data partly align with those reported in the Nuwiq EPAR (EMA/CHMP/279301/2014). E.g. among the pivotal studies, treatment success (i.e. those with an 'excellent' or 'good' rating) for minor bleeds was 98.6% in GENA-01, 100% in GENA-08, and 98.4% in GENA-03 study. For moderate to major bleeds, success rates were 91.7% (GENA-01), 100% (GENA-08), and 60.9% (GENA-03, paediatric study). No valid comparison can be made with regard to major to life threatening bleeds for which treatment success was 66.7% according to the EPAR, but this numbers was based on three bleeds only (for comparison: integrated analysis 57.5% treatment success for major to life threatening bleeds with N=23). Therefore, treatment efficacy at least for moderate to major bleeds was lower in the integrated GENA-pool analysis. However, it was clarified that deviations in the reported treatment success rates of the integrated analysis when compared to individual studies reported in the EPAR result from different age distributions, i.e. in the integrated analysis a larger proportion of paediatric patients <12 years of age was present and which had slightly lower success rates. Accordingly, age-staggered data of the integrated analysis demonstrate consistency with success rates of other relevant studies.
For surgical prophylaxis in the GENA-pool, treatment success intraoperative (n=24) was 75% (25% unknown), and postoperative 74.2-86.1% (unknown 13.9-25.0%). There was no procedure rated non-successful. The mean total number of injections (preoperative, at surgery day, intraoperative, postoperative) was 13 injections (and 8.3 EDs), the majority was administered postoperatively. It is noted that large heterogeneity among routine protocols was present at different study sites. Thus, some concerns aroused from the maximum number of postoperatively administered injections (max: 75.0, median 9.5, Q3: 14) with a maximum of 53 EDs, i.e. in 25% of the surgical procedures 14-75 injections have been administered postoperatively. Additional details on the major surgeries that required >30 post-surgical prophylactic infusions and underlying reasons for the high number of post-operative infusions were provided to rule out concerns related to surgical efficacy. Taking into account the variability of routine use of surgical prophylaxis among different study sites as well as heterogeneity of success evaluations, the data for surgical prophylaxis are considered acceptable.

In summary, efficacy data of GENA-99 and the integrated analysis are consistent with the established efficacy profile of Nuwiq.

With regards to safety of FVIII products in general, hypersensitivity reactions and immunogenicity, in particular occurrence of FVIII inhibitory antibodies, are clinically relevant safety concerns. For Nuwiq, occurrence of hypersensitivity reaction is a common adverse drug reaction, as described in the SmPC. FVIII inhibition is described with very common frequency in previously untreated patients (PUPs) and uncommon frequency in previously treated patients (PTPs) according to the Guideline on core SmPC for human plasma derived and recombinant coagulation factor VIII products rev. 3. (EMA/CHMP/BPWP/1619/1999 rev. 3). As part of the post-authorisation investigation, typically 200 PTPs with balanced age distribution should be evaluated for 100 EDs especially to cover immunogenicity aspects, implying that in case inhibitors occur at an incidence of 1.5% or higher, there is at least 95% probability to observe antibodies in one or more patients. The required study size was not achieved in GENA-99 but 216 HA patients treated prophylactically for ≥100 EDs (208 patients had severe HA) and with balanced age distribution were included in the integrated GENA-pool analysis in

order to meet regulatory standards. In GENA-99 as well as in the GENA-pool data, study procedures for FVIII inhibitor testing just partly align with the recommendations made in the EMA FVIII guideline which foresees that i) a recovery and inhibitor test in a central laboratory should confirm that the patient is inhibitor negative at study entry and ii) inhibitor and recovery testing at ED 10-15, ED50-75, and at ED~100. Of the 216 subjects included in the GENA-Pool, FVIII inhibitor testing was not done for 53 patients at screening, 62 patients between screening and completion, and 65 patients at study completion. Only a minority of the subjects have been tested consequently for inhibitors, in particular at the recommended time points of ED 10-15 (N=25/216; 11%) and ED 50-75 (N=78/216; 36%). This is essentially because the majority of the patients were in the non-interventional studies GENA-99 and GENA-100 in which FVIII inhibitor testing at set time points was not required. The MAH confirmed that a majority of patients (N=191/216; 88%) has been tested at other time points between screening and before accumulating ≥100 EDs. Additionally, it was clarified that for study GENA-99 inhibitor testing at study completion (only 26.9% of patients were tested) was hampered by the pandemic situation in 2020 (Last Patient Out was 20-Aug-2020). In conclusion, no patient in the GENA-Pool was tested positive for FVIII inhibitors or had clinical symptoms suspicious of inhibitor formation. As there is no overall indication of an increased immunogenicity risk for Nuwiq, this issue is not further pursued.

Overall, despite these identified issues, it is considered that the data presented are sufficient and confirm the favourable benefit-risk balance of Nuwiq/Vihuma.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None

Submission of the final report from study GENA-99 including the integrated analysis report of studies GENA-99, GENA-13, GENA-15, GENA-21, GENA-21b and GENA-100.

☒ is recommended for approval.

Amendments to the marketing authorisation

The worksharing procedure leads to no amendments to the terms of the Community Marketing Authorisation.

The MAH will provide the study results of GENA-21b study by Q1-2022 with an update of the SmPC to include the ADR of chest pain from GENA-21b study.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

This variation includes the submission of the final reports from study GENA-99 including the integrated analysis report of studies GENA-99, GENA-13, GENA-15, GENA-21, GENA-21b and GENA-100 to provide data on the long-term immunogenicity, safety, and efficacy of simoctocog alfa in patients with haemophilia A in line with the requirements of the FVIII guideline.

The MAH will provide the study results of GENA-21b study by Q1-2022 with an update of the SmPC to include the ADR of chest pain from GENA-21b study.

Please also refer to Scientific Discussion "Nuwiq-Vihuma-WS-2156"

For more information, please refer to the Summary of Product Characteristics.

Annex: Rapporteur's assessment comments on the type II variation

5. Introduction

Simoctocog alfa is a fourth-generation recombinant human factor VIII (rhFVIII) concentrate, indicated for the treatment and prophylaxis of bleeding in paediatric and adult patients with haemophilia A (HA, congenital factor VIII deficiency). It is co-marketed as Nuwiq by Octapharma and as Vihuma by Biotest, Marketing Authorisation Holder (MAH) for both products is Octapharma AB. Markteting authorisation (MA) for Nuwiq and Vihuma was issued on 22/07/2014 and on 13/02/2017, respectively.

The number of patients enrolled in the pre-authorisation clinical studies with rhFVIII Nuwiq was 135, which was considered adequate to provide relevant information on general safety aspects and to demonstrate the efficacy of rhFVIII in terms of its ability to restore factor VIII levels and stop or prevent bleeding. However, data from pre-authorisation studies were insufficient to estimate all aspects of therapy with FVIII products, especially with respect to immunogenicity.

The MAH submitted the final report from study GENA-99, a prospective, multinational, non-interventional post-authorisation study to document the long-term immunogenicity, safety, and efficacy of simoctocog alfa in patients with haemophilia A treated in routine clinical practice. Specifically, the study was designed to meet the requirements for post-authorisation studies as outlined in 'Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products' (EMA/CHMP/BPWP/144533/2009).

In addition, the MAH submitted an integrated analysis report of studies GENA-99, GENA-13, GENA-15, GENA-21, GENA-21b and GENA-100.

According to the Guideline (EMA/CHMP/BPWP/144533/2009), the number of patients typically needed in a post-authorisation study with FVIII to cover immunogenicity aspects is 200. In agreement with EMA in 2018, patient data from other post-authorisation studies contribute to the goal of documenting the long-term safety of treatment with simoctocog alfa in 200 previously treated patients (PTPs). Data from other Nuwiq studies whose patients met the requirement of 100 days of exposure and complied with the inclusion criteria of the GENA-99 study have been combined with data from GENA-99 in a pooled analysis to count towards the required 200 patients. Therefore, data from the interventional clinical studies GENA-13, GENA-15, GENA-21, GENA-21b completed post-authorisation were pooled with the data from the non-interventional post-authorisation studies GENA-99 and GENA-100.

6. Clinical Efficacy aspects

6.1. Methods – analysis of data submitted

GENA-99

This was a prospective, multinational, non-interventional post-authorisation study to document the long-term immunogenicity, safety, and efficacy of rhFVIII in patients with HA treated in routine clinical practice. The study period was from 21/01/2016 (First Patient In) until 20/08/2020 (Last Patient Out) and 80 patients were enrolled in 32 study centres in Argentina, Belarus, Czech Republic, Ecuador, France, Guatemala, Italy, Lithuania, Norway, Portugal, Slovakia, United Kingdom, and United States.

Inclusion Criteria:

- HA (FVIII:C ≤2%) based on medical history; at least 100 patients should have severe HA (FVIII:C <1%)
- Male patients of any age
- Previous treatment with a FVIII concentrate for more than 150 exposure days (EDs)
- Availability of detailed documentation (patient diary) covering either the last 50 EDs or the last 2 years per patient to confirm treatment modality (i.e., prophylaxis, on-demand, recent surgery, or immune tolerance induction)
- Inhibitor negative (<0.6 BU) at study entry as confirmed by a recovery test with previous FVIII product and inhibitor test
- Immunocompetence (CD4+ count >200/µL), HIV-negative, or having a viral load <200 particles/µL or <400,000 copies/mL
- Decision to prescribe Nuwiq before enrolment into the study
- Written informed consent by the patient or the patient's parent or legal guardian

Exclusion Criteria:

- Patients treated with any investigational medicinal product (IMP) except FVIII IMP within 30 days prior to the Screening Visit or patients planning to undergo treatment with any IMP other than Nuwiq were not eligible for enrolment into the study.

Nuwiq i.v. was administered as bolus. The treatment regimen (i.e., prophylactic treatment, on-demand treatment, ITI, or surgical prophylaxis) as well as the doses, dosing intervals, or dose adjustments were to be determined at the discretion of the treating physician following the common clinical practice and were to be recorded in the case report form (CRF). If deemed appropriate by the treating physician for the respective patient, options for individual adjustment of the prophylaxis regimen could be calculated from the results of a pharmacokinetics (PK) assessment.

Prophylactic Treatment: For long-term prophylaxis against bleeding in patients with severe HA, the usual doses are20 to 40 IU of factor VIII per kg body weight at intervals of 2 to 3 days. In some cases, especially in younger patients, shorter dosage intervals or higher doses may have been necessary.

On-Demand Treatment and surgical prophylaxis: The following tables could have been used to guide dosing.

Degree of haemorrhage	Factor VIII level required (%) (IU/dL)	Frequency of doses (hours) and duration of therapy (days)
Early haemarthrosis, muscle bleeding, or oral bleeding	20–40	Repeat every 12–24 hours. At least 1 day, until the bleeding episode as indicated by pain is resolved or healing is achieved.
More extensive haemarthrosis, muscle bleeding, or haematoma	30–60	Repeat infusion every 12–24 hours for 3 to 4 days or more until pain and acute disability are resolved.
Life threatening haemorrhages	60–100	Repeat infusion every 8 to 24 hours until threat is resolved.

Type of surgical procedure	Factor VIII level required (%) (IU/dL)	Frequency of doses (hours) and duration of therapy (days)
Minor surgery including tooth extraction	30–60	Every 24 hours, at least 1 day, until healing is achieved.
Major surgery	80–100 (pre- and postoperative)	Repeat infusion every 8–24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a factor VIII activity of 30% to 60% (IU/dL).

The objectives of this study were:

- To assess the long-term safety (including immunogenicity) of Nuwiq in treating or preventing bleeding episodes (BEs) in patients with HA
- To assess the long-term efficacy of Nuwiq in treating or preventing BEs in patients with HA

Study Outcome Parameters

- Long-term Immunogenicity and Safety
    - Incidence of FVIII inhibitors, with the diagnosis
        - based on clinical observations and
        - confirmed by FVIII inhibitor testing
    - Incidence of adverse drug reactions (ADRs), including hypersensitivity reactions
- Long-term efficacy of Nuwiq

Prophylactic treatment

- Annualised rate of breakthrough BEs
- FVIII consumption data
    - Number of EDs
    - Number of infusions (needed to treat a breakthrough BE)
    - FVIII IU/kg per infusion, per BE, per month, per year

On-demand treatment of bleeding episodes

- Annualised rate of BEs
- FVIII consumption data
    - Number of EDs
    - Number of infusions needed to treat a BE
    - FVIII IU/kg per infusion, per BE, per month, per year
- Assessment of the effectiveness of treatment at the end of a BE by the patient

Surgical prophylaxis

- Details of the surgical intervention
- FVIII consumption data
- Details on concomitantly administered products, including any blood or blood product transfusions or colloidal plasma substitutes (such as albumin, hydroxyl starch, dextran, or gelatine)
- Estimated and actual perioperative and postoperative bleeding volumes
- Overall assessment of the effectiveness of surgical prophylaxis by the treating physicians

Integrated Analysis across studies

The goal of study GENA-99 was to collect data on 200 previously treated male patients of any age with HA (FVIII:C ≤2%). The study was completed in 2021, with data obtained from 78 patients. In agreement with EMA in 2018, patient data from other post-authorisation studies will contribute to the goal of documenting the long-term safety of treatment with Nuwiq in 200 PTPs. Therefore, data from other Nuwiq studies whose patients meet the requirement of 100 days of exposure and comply with the inclusion criteria of the GENA-99 study have been combined with data from GENA-99 to count towards the required 200 patients.

The integrated analysis concerns studies GENA-99, GENA-13, GENA-15, GENA-21, GENA-21b, and GENA-100 (patients with ≥100 exposures days (ED)). The overall objective was to investigate the long-term safety, immunogenicity and efficacy of prophylactic Nuwiq treatment in previously treated paediatric and adult patients with HA and to ensure consistency in the long-term between the outcome from pre-authorisation clinical studies (5 studies with 135 previously treated paediatric and adult patients) and routine clinical practice. Paediatric and adult patients with moderate (1% < FVIII:C ≤2%) or severe (FVIII:C < 1%) HA who were under prophylactic treatment with Nuwiq for at least 100 EDs were included.

Data from the prospective, multinational, non-interventional post-authorisation study GENA-99 were pooled with data from interventional clinical studies that were completed following market authorisation in the EU (GENA-13, GENA-15, GENA-21 and GENA-21b) as well as with data from another non-interventional study on routine clinical practice (GENA-100). Study GENA-21b was ongoing at data base lock for this analysis, with a few patients ongoing in the sub-study extension in Japan, and GENA-100 is still ongoing; for these studies, only data as per pre-defined cut-off dates were included in pooled analysis. The cut-off date for study GENA-21b data was set to 31-05-19, for study GENA-100 data to 07-01-2021. For GENA-99 subjects who participated in previous GENA-studies (i.e. GENA-13 and GENA-15), the date of completion of the previous study was included into pooled

data to calculate the time between completion of previous study and GENA-99 screening. GENA-13 and GENA-15 are extension studies of GENA-03 and GENA-05, respectively. Inhibitor results obtained during the preceding studies were used to determine inhibitor history in the pooled analysis.

Study	Protocol Title
GENA-99	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-13	Clinical Study in Previously Treated Children with Severe Haemophilia A to Investigate the Long-Term Immunogenicity, Tolerability and Efficacy of Human-cl rhFVIII
GENA-15	Extension Study for Patients who completed GENA-05 (NuProtect) – to Investigate Immunogenicity, Efficacy and Safety of Treatment with Human-cl rhFVIII
GENA-21	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-21b	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-100	Prevention of bleeding in haemophilia A by prophylactic treatment with Octanate®, Wilate® or Nuwiq®: A prospective, multi-national, non-interventional study to evaluate routine practice prophylactic treatment schedules – NIS-Previq

Study outcome parameters

- Long-term Immunogenicity and Safety
  - Incidence of FVIII inhibitors
  - Incidence of adverse drug reactions (ADRs), including hypersensitivity reactions and thromboembolic events
- Long-term efficacy of Nuwiq
  - Prophylactic treatment
    - Annualised rate of bleeding episodes (BEs)
    - FVIII consumption data
      - Number of EDs
      - Number of infusions (needed to treat a breakthrough BE)
      - FVIII IU/kg per infusion, per BE, per month, per year
  - Treatment of bleeding episodes
    - Basic bleeding characteristics including site, cause and severity
    - Total number and frequency of bleeding episodes (spontaneous, traumatic, other) during the study
    - Frequency of bleeding episodes per year (ABR)
    - Overall efficacy rating
    - Frequency of successfully treated bleeding episodes (excellent and good efficacy rating)

- The number of infusions needed to treat a BE, the number of EDs and study drug consumption data (Nuwiq IU/kg per infusion, per ED and BE) per subject and in total were evaluated

- Surgical prophylaxis
  - Number of surgeries by severity category (minor, major, total)
  - Details on treatment for surgical prophylaxis (number of exposure days and injections prior to surgery, dosing details, total amount of Nuwiq
  - Details on treatment with Nuwiq pre-, intra- and post-operatively (number of exposure days and injections, dosing details, total amount of Nuwiq)
  - Evaluation of blood loss
  - Overall haemostatic efficacy evaluation at the end of surgical treatment period.
  - FVIII plasma levels in the context of the surgery

6.2. Results

Gena-99

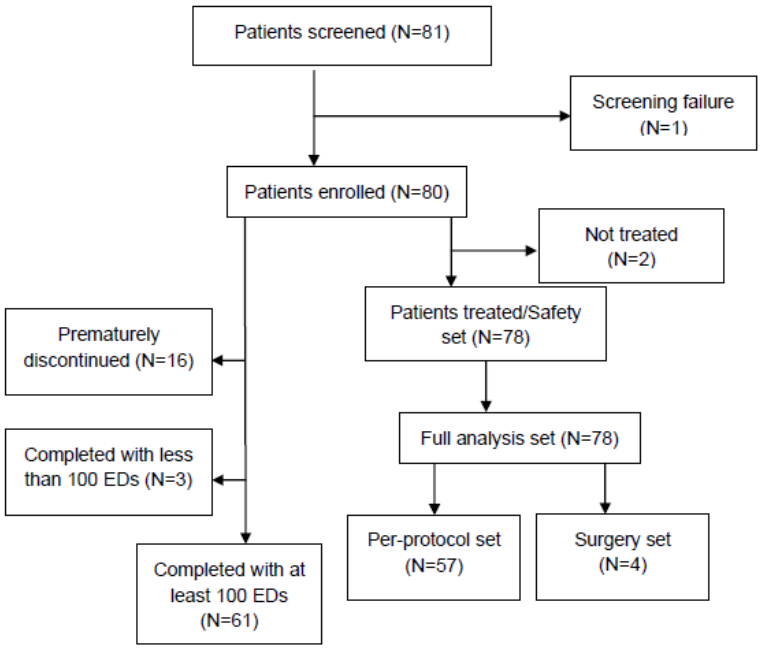
A total of 78 patients received Nuwiq in this study and were included in the analyses (safety and full analysis sets).

***Assessor's comment*:** The goal of the study was to collect data in 200 PTPs with HA (FVIII:C ≤2%). The study was completed in 2021, with data obtained from 78 patients. The MAH has stated that in agreement with EMA in 2018, patient data from other post-authorisation studies will contribute to the goal of documenting the long-term safety of treatment with Nuwiq in 200 PTPs. However, no reference regarding this agreement has been made. The MAH is asked for clarification.

40 patients (51.3%) were aged <12 years, 12 (15.4%) were 12–<18 years, and 26 (33.3%) were ≥18 years. 10 patients (12.8%) had moderate haemophilia and 68 patients (87.2%) had severe haemophilia. 61 patients (78.2%) were White, 7 (9.0%) were American Indian or Alaska Native, 1 (1.3%) was Black or African American, and 9 (11.5%) had race documented as "other". 25 patients (32.1%) identified as Hispanic or Latino. Overall, 47 (60.3%) patients had a family history of haemophilia and the most common FVIII gene defect was intron 22 inversion (17 patients [21.8%]). A total of 10 patients (12.8%) had a history of FVIII inhibitors. Mean BMI was 20.9 kg/m^2. All but 2 patients were on prophylactic treatment in the 6 months before screening. The median ABR in the 6 months before screening was 2 (range: 0-36), mean ABR was 4.3 (SD 6.82). Of note, mean ABR was notable higher in patients with moderate haemophilia (mean 9.0, SD 13.57) than in patients with severe haemophilia (mean 3.6, SD 4.96).

A total of 77 patients received prophylactic treatment (mean duration 42.7 weeks with a mean number of 113.6 infusions, for any reason). 2 patients received on-demand treatment during the study, one of whom switched between prophylactic and on-demand treatment regimen and is counted under both treatment classes.

Figure 1 Patient Disposition and Analysis Populations



ED = exposure day.

Table 6: Analysis Populations by Age Class (All Enrolled Patients, N=80)

Population	Age group						Total	
	<12 years		12 - <18 years		≥18 years			
	n	%	n	%	n	%	n	%
Enrolled	40	50.0	12	15.0	28	35.0	80	100.0
Safety Set (SAF)	40	50.0	12	15.0	26	32.5	78	97.5
Full Analysis Set (FAS)	40	50.0	12	15.0	26	32.5	78	97.5
Per-Protocol Set (PP)	30	37.5	9	11.3	18	22.5	57	71.3
Surgery Set (SURG)	3	3.8	0	0.0	1	1.3	4	5.0

Source: Table 14.1-4

21 patients were excluded from the PP population (N=57) because of major deviations (most common major deviation was patient completion/discontinuation with less than 100 EDs for 17 patients). A total of 64 patients completed the study, 61 patients with at least 100 EDs and 3 patients with less than 100 EDs.

Table 11: Extent of Exposure (All Reasons) to *Nuwiq*® for Patients Receiving Prophylaxis (N=77)

Parameter	n (Pts)	Mean	SD	Median	Range
Months in study	77	10.5	4.20	10.0	1.7–31.6
Weeks under prophylaxis	77	42.7	15.23	42.3	0.1-92.1
Number of EDs	77	111.7	38.92	109	1–195
Number of infusions	77	113.6	40.84	110.0	1–242
Average dose (IU/kg) per ED	77	39.5	15.73	37.0	16.9–111.7
Average dose (IU/kg) per infusion	77	38.7	14.64	36.83	16.9-100.7

ED=exposure day; IU=international unit; Pts= patients; SD = standard deviation.
Source: Table 14.2.1-1

Efficacy Results - Gena-99

Prophylaxis: The most commonly planned treatment regimen were three-times per week (32 [41.0%] patients), every other-day (18 [23.1%] patients), and two-times per week (17 [21.8%] patients). The planned treatment regimen at screening was on-demand for 2 (2.6%) patients. A total of 61 patients completed the study with at least 100 EDs.

A total of 252 BEs occurred in 74 patients with at least 3 months under prophylactic regimen (FAS). The median (IQR) ABRs in this study for patients with at least 3 months under prophylaxis (N=74) were 2.39 (0, 4.87) for all BEs, 0.00 (0, 2.47) for spontaneous BEs, and 0.00 (0, 1.93) for traumatic BEs. The median total ABR was slightly higher in adolescents (3.34 [1.17, 4.66]) compared to younger children (1.95 [0, 5.46]) and adults (1.52 [0, 4.35]), but the sample size was small in adolescents (N=12). When BEs were analyzed by disease severity, the median total ABR was 3.85 (range 0-6.04, mean 5.02, SD 6.08) for moderate haemophilia (N=10 patients) and 2.21 (range 0-4.41, mean 3.94, SD 6.56) for severe haemophilia (N=64). It is noted that there were only 10 patients with moderate haemophilia and these patients received on average ~ 35% lower amounts of Nuwiq per month. The median total ABR observed on-study in patients with at least 3 months under prophylaxis was consistent with the ABR in the 6 months prior to the study: 2.0 (0,6.00).

Table 13: Extent of Prophylactic Exposure to *Nuwiq*® by Haemophilia Severity (Patients With at Least 3 Months Under Prophylaxis, N=74)

Parameter	Statistic	Moderate Haemophilia n (Pts)=10	Severe Haemophilia n (Pts)=64
Weeks under prophylaxis	Mean (SD) Median (range)	49.3 (16.95) 38.9 (36.7-77.7)	43.5 (12.64) 42.7 (16.0-92.1)
Months under prophylaxis	Mean (SD) Median (range)	11.3 (3.90) 8.9 (8.4-17.9)	10.0 (2.91) 9.8 (3.7-21.2)
Number of EDs	Mean (SD) Median (range)	111.9 (29.65) 106.0 (70-154)	109.2 (34.38) 103.0 (29-193)
Number of infusions	Mean (SD) Median (range)	112.0 (29.61) 106.5 (70-154)	110.1 (36.72) 103.0 (29-242)
Average dose (IU/kg) per ED	Mean (SD) Median (range)	29.2 (8.89) 29.3 (13.5-40.0)	40.1 (15.32) 37.0 (16.9-103.0)
Average dose (IU/kg) per infusion	Mean (SD) Median (range)	29.2 (8.90) 29.3 (13.5-40.0)	39.8 (15.14) 37.0 (16.9-101.9)
Average dose (IU/kg) per month	Mean (SD) Median (range)	302.3 (127.68) 254.1 (123.3-525.9)	470.6 (285.35) 415.5 (99.3-1616.1)

ED=exposure day; IU=international unit; Pts= patients; SD = standard deviation.

Table 14: Annualised Bleeding Rates in Patients With at Least 3 Months Under Prophylaxis (FAS, N=74)

	Mean	SD	Median	Range	IQR
ABR, spontaneous BEs					
<12 years (n=49, N=40)	1.45	3.318	0.00	0-15.5	0-1.31
12–<18 years (n=30, N=12)	2.89	5.984	0.48	0-21.0	0-2.73
≥18 years (n=59, N=22)	2.83	4.441	1.10	0-17.7	0-3.13
Total (n=138, N=74)	2.09	4.176	0.00	0-21.0	0-2.47
ABR, traumatic BEs					
<12 years (n=88, N=40)	2.89	6.422	0.00	0-37.1	0-3.57
12–<18 years (n=10, N=12)	1.05	1.432	0.00	0-3.5	0-2.17
≥18 years (n=8, N=22)	0.37	1.121	0.00	0-4.6	0-0
Total (n=106, N=74)	1.84	4.904	0.00	0-37.1	0-1.93
ABR, all BEs					
<12 years (n=140, N=40)	4.41	7.404	1.95	0-38.7	0-5.46
12–<18 years (n=45, N=12)	4.61	6.569	3.34	0-24.5	1.17-4.66
≥18 years (n=67, N=22)	3.20	4.466	1.52	0-17.7	0-4.35
Total (n=252, N=74)	4.09	6.471	2.39	0-38.7	0-4.87

ABR = annualised bleeding rate, BE = bleeding episode, IQR = interquartile range, n = number of BEs, N= number of patients, SD = standard deviation

***Assessor's comment*:** As noted, the mean and median ABR in the 6 months before screening was 4.3 (SD 6.82) and 2 (range: 0-36), respectively. These data align with the prophylactic ABR results of study GENA-99. Of note, the ABR measure lacks sensitivity when it comes to the comparison of bleeding frequencies in the low-digit range. Overall, the presented data reflect usual exposure during prophylactic treatment, and a typically low bleeding frequency with high dispersion.

Treatment of bleeding episodes: Of the 77 patients in the FAS population who received prophylaxis with Nuwiq, 49 patients experienced a total of 255 treatment-emergent BEs; 28 (36.4%) patients had no treatment emergent BEs. No major or life-threatening BEs occurred; 161 (63.1%) of the treatment-emergent BEs were minor and 94 (36.9%) were moderate to major. The severity of treatment-emergent BEs was also presented by site of bleeding and type of BE. The majority of moderate to major bleeds, i.e. 62/94 bleeds (53%) were joint bleeds, throughout all age classes.

246 treatment-emergent BEs in 48 patients occurred under prophylactic regimen and were treated with Nuwiq (133 spontaneous, 105 traumatic, 1 postoperative, 5 'other', 2 had missing type; 117 occurred in joints, 128 were non-joint, and 1 had unknown site). The median number of infusions per BE was 1.0 (IQR: 1.00, 2.00; range: 1-24), and the median dose per infusion per BE/kg body weight was 35.65 IU/kg (IQR: 27.78, 42.64; range: 14.0-76.1).

Table 15: EDs and *Nuwiq*® Dosages for Treatment of Treatment-Emergent BEs (246 BEs in 48 Patients)

Parameter	Mean	SD	Median	Range	IQR
Number of injections per bleeding episode	1.78	2.024	1.00	1-24	1-2
Number of EDs per bleeding episode	1.61	1.466	1.00	1-17	1-2
Dose of *Human-cl rhFVIII* per BE, IU	2868.90	5273.813	2000.00	250-69500	1000-3000
Dose of *Human-cl rhFVIII* per BE, IU/kg	66.86	90.495	44.94	14-1139	32.47-65.36
Dose of *Human-cl rhFVIII* per infusion per BE, IU	1537.93	996.149	1500.00	250-8000	625–2000
Dose of *Human-cl rhFVIII* per infusion per BE, IU/kg	36.72	12.346	35.65	14-76	27.78–42.64
Dose of *Human-cl rhFVIII* per ED per BE, IU	1621.08	1068.149	1666.70	250-8000	625–2000
Dose of *Human-cl rhFVIII* per ED per BE, IU/kg	39.00	15.689	35.71	14-99	27.78–46.51

BE = bleeding episode; ED = exposure day; IQR = interquartile range; IU = international unit; SD = standard deviation.

Table 16: Treated Bleeding Episodes by Site (246 BEs in 48 Patients)

Site of bleeding	n	%
Knee Joint	74	30.1
Ankle Joint	30	12.2
Elbow Joint	13	5.3
Nose	13	5.3
Leg	13	5.3
Arm	12	4.9
Oral Cavity	7	2.8
Intestinal	3	1.2
Unknown	1	0.4
Other	80	32.5
Total	246	100.0

n=number of bleeding episodes (BEs)
Source: Table 14.2.2.1.2-2

Most BEs that occurred under prophylaxis (210 [85.4%]) were resolved with 1 (168 BEs) or 2 (42 BEs) infusions of Nuwiq. One patient had a BE with duration of 18 days with efficacy rated as "none" (see below).

The efficacy assessment of bleeding episodes at end of a BE was evaluated on a 4-point scale by the patient/legal guardian (together with the Investigator in case of on-site treatment).

Table 17: Efficacy Assessment (Final Outcome) of Treatment of Bleeding Episodes Using a Four-point Scale (246 BEs in 48 Patients)

	Number (%) of BEs
Rating	**N=246**
Excellent	167 (67.9)
Good	50 (20.3)
Moderate	26 (10.6)
None	3 (1.2)
Success	217 (88.2)
Non-success	29 (11.8)

Success = efficacy rating of excellent or good, Non-Success = efficacy rating of moderate or none.
BE = bleeding episode.

The majority of BEs were rated as having excellent (67.9%) or good (20.3%) treatment efficacy, giving a success rate of 88.2%. Treatment efficacy was rated as moderate for 26 (10.6%) BEs and as none for 3 (1.2%) BEs. Of the treated spontaneous BEs (N=133), the majority were rated as having excellent (71.4%) or good (21.8%) treatment efficacy, giving a success rate of 93.2%. Treatment efficacy was rated as moderate for 6 (4.5%) spontaneous BEs and as none for 3 (2.3%) spontaneous BEs. For comparison, the MAH stated that treatment success rate in interventional studies averaged at 85% (93.2% for spontaneous BEs).

The 3 spontaneous BEs with efficacy rated as none were described as follows:

- A moderate to major spontaneous BE in the left knee of one patient that was treated with 24 infusions of Nuwiq (11 with 65.6 IU/kg, 8 with 32.8, 2 with 49.13, 2 with 16.4, and 1 with 24.6). The BE lasted 18 days and he tested negative for FVIII inhibitors at the end of this BE. This patient discontinued the trial prematurely at his own request following this BE, with a total of 34 EDs.
- A moderate to major spontaneous BE in the left elbow in one patient that was treated with 10 infusions of Nuwiq. The BE lasted 7 days. Subsequent BEs in this patient were treated with excellent, good or moderate efficacy. This patient completed the study according to protocol with 182 EDs and he tested negative for FVIII inhibitors at study completion.
- A moderate to major spontaneous BE in the left knee of one patient that was treated with 4 infusions of Nuwiq and was ongoing at end of study. This patient completed the study according to protocol, with 183 EDs. There was no suspicion of inhibitor formation.

***Assessor's comment*:** The MAH is requested to further clarify the numerical high range of injections per treatment-emergent bleeding episode (1-24) and EDs (1-17). A detailed narrative of the three non-responding patients, in particular of the patient treated with 24 infusions, should be provided along with a critical expert statement.

On-demand: 2 patients were treated on-demand during the study. One patient switched between on-demand and prophylactic. He was treated on-demand for 21.7 months, during which he experienced 22 BEs. These BEs were treated with a total of 26 infusions of Nuwiq on 26 EDs, with a mean dose of 29.9 IU/kg per infusion, 1 with moderate, 4 with good and 17 with excellent efficacy. Another patient received only on-demand treatment and was treated for 11.8 months, during which he experienced 33 BEs. These BEs were treated with a total of 40 infusions of Nuwiq on 38 EDs, with a mean dose of 21.8 IU/kg per infusion, all with excellent efficacy.

Surgical prophylaxis: A total of 4 patients had 6 surgeries that were treated with Nuwiq. Two of these surgeries were minor and 4 were major. Five surgeries had an overall efficacy assessment performed jointly by the hematologist and surgeon, all rated as having excellent efficacy. One of the six surgeries was treated pre-op with Advate and post-op with Nuwiq and therefore no efficacy assessment of Nuwiq efficacy could be performed. One patient had 1 surgery that was not treated with Nuwiq.

Table 18: Surgeries: description, total dose and outcome of surgical procedures

Surgery No.	Description of surgery	Type of surgery	Number of Nuwiq® Infusions	Actual/ average expected blood loss	Overall Efficacy Assessment of Prophylaxis[1]
1	Dental extraction (planned)	Minor	0 pre-op 0 post-op	0/0 mL	Not applicable
1	Port removal and reinsertion (emergency)	Minor	1 pre-op 9 post-op	0/0 mL	Excellent
1	Hip prothesis (planned)	Major	1 pre-op 11 post-op	Not done	Excellent
1	Right knee synovectomy (planned)	Major	1 pre-op 22 post-op	5/5 mL	Excellent
2	Removal of left chest wall port a-cath and placement of temporary subclavian central venous catheter (planned)	Major	0 pre-op 3 post-op	Not done	Not applicable
3	Placement of a 6.6 French port (planned)	Major	1 pre-op 0 post-op	Not done	Excellent
1	Port removal (planned)	Minor	1 pre-op 2 post-op	Not done	Excellent

[1] Performed jointly by hematologist and surgeon

***Assessor's comment*:** Additional explanation is requested for the surgical efficacy ratings. For 3/5 rated procedures data for actual vs. expected blood loss are not available. Two rated procedures where a minor surgery of port removal, one with reinsertion with post-op 9 infusions whereas the other patient received only 2 infusion post-op. Additionally, one patient with right knee synovectomy (major surgery) with actual blood loss of 5 ml had 11 infusion of Nuwiq post-op.

It is thus unclear on which basis excellent ratings could have been achieved.

Integrated analysis

A total of 216 patients were under prophylaxis with Nuwiq for at least 100 EDs and were included in the POOL set (GENA-13, N=49; GENA-15, N=39, GENA-21, N=25, GENA-21b, N=25, GENA-99, N=61; GENA-100, N=17). Of the 216 patients in the GENA-POOL, 123 (56.9%) were aged <12 years, 17 (7.9%) were aged 12-<18 years, and 76 (35.2%) were aged ≥18 years. Age at screening in the GENA-POOL ranged from 1 to 71 years, with a median of 8 years. Eight (3.7%) patients had moderate haemophilia A and 208 (96.3%) had severe haemophilia A. A total of 183 (84.7%) patients were White, 19 (8.8%) were Asian, 5 (2.3%) were American Indian or Alaska Native, 1 (0.5%) was Black or African American, and 8 (3.7%) had race documented as "other". Twenty patients (9.3%) identified as Hispanic or Latino. Overall, 69 (31.9%) patients had a family history of haemophilia and 9 (4.2%) patients had a family history of FVIII inhibitors. A total of 15 (6.9%) patients had a history of FVIII inhibitors. It was concluded that the GENA-POOL patient population met the requirements outlined in Guideline EMA/CHMP/BPWP/144533/2009 as it included 208 patients with severe haemophilia A, 123

patients aged <12 years and 17 aged 12-<18 years, and 6.9% patients had a history of FVIII inhibitors.

In GENA-POOL patients had a mean of 18.7 months under treatment with Nuwiq and received a mean of 233.6 infusions with a mean dose of 38.3 IU/kg per infusion (for any reason).

Table 4: Planned Nuwiq® treatment regimen at screening/baseline by age class, GENA-POOL (POOL, N=216)

Regimen	Age Class							
	<12 Years		12-<18Years		≥18 Years		Total	
	N	%	N	%	N	%	N	%
1 Time per Week	6	4.88	0	0.00	0	0.00	6	2.78
2 Times per Week	38	30.89	1	5.88	6	7.89	45	20.83
3 Times per Week	38	30.89	9	52.94	53	69.74	100	46.30
4 Times per Week	1	0.81	0	0.00	0	0.00	1	0.46
BID	1	0.81	0	0.00	0	0.00	1	0.46
Every 3 Days	1	0.81	1	5.88	2	2.63	4	1.85
QD	0	0.00	0	0.00	2	2.63	2	0.93
QOD	35	28.46	5	29.41	12	15.79	52	24.07
Unknown	3	2.44	1	5.88	1	1.32	5	2.31
Total	123	100.00	17	100.00	76	100.00	216	100.00

BID = twice daily; POOL = pooled set; QD = once a day; QOD = every other day; yrs = years.
For subjects from study GENA-100 who were under prophylaxis with Octanate® or Wilate® at screening, treatment regimen at the time of switch to Nuwiq® was taken as baseline
Source: Tables 14.1-20

Table 6: Extent of Exposure (All Reasons) to *Nuwiq*® GENA-POOL (POOL, N=216)

Parameter	n (Pts)	Mean	SD	Median	Range
Months under treatment	216	18.7	10.54	16.8	5.9–55.1
Number of EDs	216	230.5	150.50	172.5	100–807
Number of infusions	216	233.6	154.28	185.0	100–906
Average dose (IU/kg) per ED	216	38.9	13.39	35.9	16.6–111.7
Average dose (IU/kg) per infusion	216	38.3	12.79	35.71	16.6-100.7

ED=exposure day; IU=international unit; POOL = pooled set; Pts= patients; SD = standard deviation.
Source: Table 14.2.1-1

Efficacy Results - Integrated analysis

The most commonly employed prophylactic treatment regimen in the GENA-POOL (each patient could have had multiple prophylactic treatment regimens while on the study) were three-times-per-week (109 [39.9%] patients), every-other-day (61 [22.3%] patients), and two-times-per-week (57 [20.9%]). The mean duration of prophylactic treatment in the GENA-POOL was 18.7 months, ranging from 5.9 to 55.1 months. The mean dose (±SD) per kg per infusion for prophylaxis was 38.2 ± 12.9 IU/kg (median: 35.4 IU/kg; range, 13.5–101.9), with higher average doses in patients aged <12 years, in line with the Nuwiq SPC which recommends a dose range of 20–40 IU/kg, with the regimen to be adjusted based on patient response and higher dosages to be considered in younger patients.

Table 9: Extent of Prophylactic Exposure to *Nuwiq*, GENA-POOL (POOL, N=216)

Parameter	Statistic	<12 years n (Pts)=123	12 - <18 years n (Pts)=17	≥18 years n (Pts)=76	Total n (Pts)=216
Months under prophylaxis	Mean (SD)	21.8 (9.29)	20.0 (12.47)	13.4 (10.02)	18.7 (10.54)
	Median (range)	23.8 (5.9-54.6)	15.4 (6.9-53.2)	9.3 (7.2-55.1)	16.8 (5.9-55.1)
Number of EDs	Mean (SD)	254.9 (134.08)	254.9 (181.98)	154.2 (128.46)	219.5 (144.03)
	Median (range)	215.0 (78-570)	190.0 (95-709)	112.0 (68-709)	161.0 (68-709)
Number of infusions	Mean (SD)	255.5 (134.14)	255.2 (182.14)	155.3 (132.80)	220.2 (145.37)
	Median (range)	217.0 (78-570)	190.0 (96-709)	112.0 (68-779)	161.0 (68-779)
Average dose (IU/kg) per ED	Mean (SD)	39.8 (14.30)	31.3 (6.11)	37.6 (11.50)	38.3 (13.05)
	Median (range)	36.3 (13.5-103)	33.3 (17.8-38.4)	35.2 (17.5-85.8)	35.4 (13.5-103)
Average dose (IU/kg) per infusion	Mean (SD)	39.7 (14.20)	31.3 (6.09)	37.5 (11.32)	38.2 (12.93)
	Median (range)	36.3 (13.5-102)	33.3 (17.8-38.4)	35.2 (17.5-85.4)	35.4 (13.5-101.9)
Average dose (IU/kg) per month	Mean (SD)	482.7 (262.91)	390.5 (107.48)	437.4 (217.42)	459.5 (239.64)
	Median (range)	436.5 (112-1616)	420.4 (155-524)	407.2 (199-1966)	423.0 (112-1966)

ED=exposure day; IU=international unit; POOL = pooled set; Pts= patients; SD = standard deviation.
Source: Table 14.2.3.1-1

***Assessor's comment*:** For the complete GENA-pool including all age groups (N=216), median prophylactic dosing per injection was 35.41 IU/kg (third quartile Q3: 43.41 IU/kg, max: 101.9 IU/kg) and per ED 35.41 IU/kg (Q3: 43.52 IU/kg, max: 103 IU/kg). For the age class ≥ 18 years (N=76), median prophylactic dosing per injection was 35.17 IU/kg (Q3: 42.55 IU/kg; max: 85.4 IU/kg). For the age class <12 years (N=123), median prophylactic dosing per injection was 36.33 IU/kg (Q3: 44.12 IU/kg; max: 101.9 IU/kg). Data are derived from Table 14.2.3.1-1. It appears that a considerable portion, i.e. about a quarter of the patients (adults as well as paediatrics), received higher than the recommended usual prophylactic dosing (20 to 40 IU/kg) with maximum 2-fold of the recommended prophylactic dosing. A detailed clarification is requested.

Annualised Bleeding Rates During Prophylactic Treatment: Of the 216 patients in the GENA-POOL, 160 (74.1%) patients experienced a total of 1111 treatment-emergent BEs; 56 (25.9%) patients had no treatment-emergent BEs. Of the 1111 treatment-emergent BEs, 572 (51.5%) were minor, 492 (44.3%) were moderate to major, 41 (3.7%) were major to life-threatening, and 6 (0.5%) were of unknown severity. The mean (SD) and median (IQR) ABRs in the GENA-POOL were 3.92 (8.42) and 1.78 (0, 4.24) for all BEs, 1.89 (4.7) and 0.11 (0, 1.45) for spontaneous BEs, and 1.80 (4.73) and 0.50 (0, 1.95) for traumatic BEs.

Table 11: Annualised Bleeding Rates Under Prophylaxis, GENA-POOL (POOL)

Parameter/Age group	Mean	SD	Median	Range	IQR
ABR, spontaneous BEs					
<12 years (n=148, N=123)	0.82	2.076	0.00	0-15.5	0-0.85
12–<18 years (n=46, N=17)	2.38	5.039	1.13	0-21.0	0-1.77
≥18 years (n=270, N=76)	3.52	6.854	1.19	0-48.4	0-4.13
Total (n=464, N=216)	1.89	4.726	0.11	0-48.4	0-1.45
ABR, traumatic BEs					
<12 years (n=414, N=123)	2.06	4.253	0.69	0-37.1	0-2.10
12–<18 years (n=44, N=17)	1.41	1.470	1.21	0-4.1	0-2.47
≥18 years (n=107, N=76)	1.46	5.846	0.00	0-49.6	0-1.29
Total (n=565, N=216)	1.80	4.736	0.50	0-49.6	0-1.95
ABR, all BEs					
<12 years (n=620, N=123)	3.13	5.406	1.46	0-38.7	0-3.19
12–<18 years (n=100, N=17)	4.13	5.595	3.13	0-24.5	2.34-4.95
≥18 years (n=391, N=76)	5.17	12.112	2.25	0-100.5	0-5.53
Total (n=1111, N=216)	3.92	8.426	1.78	0-100.5	0-4.24

ABR = annualised bleeding rate; BE = bleeding episode; IQR = interquartile range; n = number of BEs; N= number of patients; POOL = pooled set; SD = standard deviation
Source: Table 14.2.3.2-5

Table 12: Total Annualised Bleeding Rates Under Prophylaxis, by Study

	n, N median (IQR)						
	Study						
Parameter/Age group	-13	-15	-21	-21b	-99	-100	Pool
<12 years	281, 43 **1.56** (0.53-2.72)	120, 39 **1.00** (0-1.96)	Not included	Not included	116, 33 **2.08** (0-4.47)	103, 8 **4.99** (1.56-8.96)	620, 123 **1.46** (0-3.19)
12–<18 years	54, 6 **3.71** (0-4.95)	Not included	Not included	Not included	42, 10 **3.34** (2.34-3.64)	4, 1 **2.60** (2.60-2.60)	100, 17 **3.13** (2.34-4.95)
≥18 years	Not included	Not included	139, 25 **1.25** (0-3.79)	152, 25 **4.41** (2.24-7.63)	61, 18 **2.28** (0-4.35)	39, 8 **1.19** (0.82-1.56)	391, 76 **2.25** (0-5.53)
Total	355, 49 **1.72** (0.53-3.14)	120, 39 **1.00** (0-1.96)	139, 25 **1.25** (0-3.79)	152, 25 **4.41** (2.24-7.63)	219, 61 **2.44** (0-4.35)	146, 17 **1.74** (1.12-4.14)	1111, 216 **1.78** (0-4.24)

IQR = interquartile range; n = number of BEs; N= number of patients
Source: Table 14.2.3.2-5

When BEs were analysed by disease severity, the mean (SD) and median (range) total ABR in the GENA-POOL was 5.59 (6.61) and 3.85 (0, 9.69) for moderate HA, and 3.86 (8.5) and 1.73 (0, 4.18) for severe HA. It is argued that only 8 patients with moderate haemophilia A were included (all in GENA-99) and these patients received lower amounts of Nuwiq per month on average (322.6 vs 464.8 IU/kg/month).

***Assessor's comment*:** The MAH has noted that caution is required when comparing ABR data between different studies, but the ABRs in each study indicate good bleeding control with Nuwiq prophylaxis when compared to the median ABR of 54.5 observed with on-demand Nuwiq treatment in study GENA-01. It is endorsed that ABR estimates generally lack sensitivity when it come to the comparison of prophylactically treated patients. Nevertheless, among the individual studies in the GENA-pool, the GENA-21b study showed notable higher ABR frequencies. The MAH is asked to provide a possible explanation for this observation.

Analysis of the efficacy of treatment of bleeding episodes that occurred under prophylaxis: A total of 1011 treatment-emergent BEs in 152 patients in the GENA-POOL were treated with Nuwiq; 410 were

spontaneous, 532 were traumatic, 7 were postoperative, 29 were 'other', and 33 had missing type. 507 BEs occurred in joints, 497 were non-joint, and 7 had unknown site. The mean and median number of Nuwiq infusions per BE was 1.7 (SD 1.6) and 1.0 (IQR: 1.00, 2.00; range: 1-16). The mean and median dose per infusion per BE/kg body weight was 39.9 IU/kg (SD 15.8) and 35.97 IU/kg (IQR: 30.30, 45.45; range: 12.6-118).

Table 13: EDs and *Nuwiq*® Dosages for Treatment of Treatment-Emergent BEs, GENA-POOL (1011 BEs in 152 Patients)

Parameter	Mean	SD	Median	Range	IQR
Number of injections per bleeding episode	1.70	1.565	1.00	1-16	1-2
Number of EDs per bleeding episode	1.57	1.318	1.00	1-16	1-2
Dose of *Human-cl rhFVIII* per BE, IU	3131.26	3719.923	2000.00	250-35250	1000-4000
Dose of *Human-cl rhFVIII* per BE, IU/kg	65.44	58.294	45.45	12.6-490	32.89-74.35
Dose of *Human-cl rhFVIII* per infusion per BE, IU	1857.54	1127.419	2000.00	167-6250	1000–2500
Dose of *Human-cl rhFVIII* per infusion per BE, IU/kg	39.90	15.834	35.97	12.6-118	30.30–45.45
Dose of *Human-cl rhFVIII* per ED per BE, IU	1995.36	1387.382	2000.00	250-12000	1000–2500
Dose of *Human-cl rhFVIII* per ED per BE, IU/kg	42.22	18.195	37.04	12.6-171.4	30.63–47.96

BE = bleeding episode; ED = exposure day; IQR = interquartile range; IU = international unit; SD = standard deviation.

Source: Table 14.2.2.2.1-1

The median duration of treated BEs in the GENA-POOL was 1.0 day (range: 1-14 days). Most BEs (860 [85.1%]) were resolved with 1 (710 BEs) or 2 (150 BEs) infusions of Nuwiq. Efficacy was assessed using a 4-point scale. The majority of BEs in the GENA-POOL were rated as having excellent (54.2%) or good (30.1%) treatment efficacy, giving a success rate of 84.3%. Treatment efficacy was rated as moderate for 123 (12.2%) BEs and as none for 15 (1.5%) BEs. The success rate for spontaneous BEs was 83.4%.

Table 15: Efficacy Assessment (Final Outcome) of Treatment of Bleeding Episodes Using a Four-point Scale

Rating	Number (%) of BEs						
	-13 N=310	-15 N=105	-21 N=139	-21b N=125	-99 N=211	-100 N=121	Pool N=1011
Excellent	178 (57.4)	56 (53.3)	44 (31.7)	44 (35.2)	141 (66.6)	85 (70.2)	548 (54.2)
Good	74 (23.9)	25 (23.8)	83 (59.7)	47 (37.6)	44 (20.9)	31 (25.6)	304 (30.1)
Moderate	46 (14.8)	20 (19.0)	9 (6.5)	20 (16.0)	24 (11.4)	4 (3.3)	123 (12.2)
None	6 (1.9)	3 (2.9)	3 (2.2)	1 (0.8)	2 (0.9)	0 (–)	15 (1.5)
Unknown	6 (1.9)	1 (1.0)	0 (–)	13 (10.4)	0 (–)	1 (0.8)	21 (2.1)
Success	252 (81.3)	81 (77.1)	127 (91.4)	91 (72.8)	185 (87.7)	116 (95.9)	852 (84.3)
Non-success	52 (16.8)	23 (21.9)	12 (8.6)	21 (16.8)	26 (12.3)	4 (3.3)	138 (13.6)

Success = efficacy rating of excellent or good; Non-Success = efficacy rating of moderate or none.
BE = bleeding episode.
Source: Table 14.2.2.2.3-1

Table 14.2.2.2.3-5
Overall efficacy assessment of treatment including success by severity of bleeding and age class (frequency distribution)
(Subjects included in pooled set (POOL) with treated BEs, N=152)
GENA-Pool subjects with treated BEs/number of treated BEs, N=152/n=1011

Age Class: Total

Severity of Bleeding	Overall Efficacy Assessment of Treatment										Total		Success[2]						Total	
	Excellent		Good		Moderate		None		Unknown				Success		Non-Success		Unknown			
	n[1]	%	n[1]	%	n[1]	%	n[1]	%	n[1]	%	n[1]	%	n[1]	%	n[1]	%	n[1]	%	n[1]	%
Minor	362	73.6	91	18.5	27	5.5	1	0.2	11	2.2	492	100.0	453	92.1	28	5.7	11	2.2	492	100.0
Moderate to Major	180	37.9	194	40.8	81	17.1	14	2.9	6	1.3	475	100.0	374	78.7	95	20.0	6	1.3	475	100.0
Major to Life-threatening	5	12.5	18	45.0	15	37.5	0	0.0	2	5.0	40	100.0	23	57.5	15	37.5	2	5.0	40	100.0
Unknown	1	25.0	1	25.0	0	0.0	0	0.0	2	50.0	4	100.0	2	50.0	0	0.0	2	50.0	4	100.0
Total	548	54.2	304	30.1	123	12.2	15	1.5	21	2.1	1011	100.0	852	84.3	138	13.6	21	2.1	1011	100.0

[1]Number of treated bleeding episodes under Nuwiq® treatment
[2]Bleeding episodes with efficacy rating assessed as 'excellent' or 'good' are considered 'successfully treated'

***Assessor's comments*:** Treatment success rates for BE occurring under prophylactic treatment were 92.1% for minor, 78.7% for moderate to major, and 57.5% for major to life-threatening bleeds (overall treatment success was 84.3%). These data just partly align with those reported in the Nuwiq EPAR (EMA/CHMP/279301/2014). E.g. for moderate to major bleeds among the pivotal studies treatment success rates were 91.7% (GENA-01), 100% (GENA-08), and 60.9% (GENA-03). Thus, treatment efficacy for moderate to major bleeds appears to be somewhat lower in the integrated GENA-pool analysis. The MAH should comment on the clinical significance of this observation.

Surgical prophylaxis: In the GENA-POOL, a total of 31 patients had 51 surgeries that were treated with Nuwiq. 15 of these surgeries were minor, 21 were major, and 15 had unknown severity (severity was not collected in study GENA-100). 45/51 surgeries were planned and 6/51 were emergency.

The median total dose of Nuwiq administered for surgery in the GENA-POOL was 399.99 IU/kg with a median of 9 infusions (range: 1-76) and a median of 36.06 IU/kg (max: 96.5 IU/kg) Nuwiq per infusion.

***Assessor's comments*:** For the 51 surgeries, there was a mean total (preoperative, at surgery day, intraoperative, postoperative) number of 13 injections and 8.3 EDs, with the majority in the postoperative stage. The maximum number of postoperative injections was 75.0 (median 9.5, Q3: 14) with a maximum of 53 EDs (median: 6.00, Q3: 9.00). I.e. in 25% of the surgical procedures 14-75 injections have been administered postoperatively. This range appears unusual high and the MAH is requested for clarification.

The median actual blood loss of 7.5 mL (IQR: 0, 32.5) was lower than the median expected average blood loss of 10.0 mL (IQR: 5, 50.0). For study GENA-100, blood loss was assessed based on expectedness categories; 5 surgeries had blood loss that was as expected, with 10 surgeries having no blood loss. No surgical procedure was assessed as having non-successful Nuwiq treatment. Of note, treatment success was unknown in 14-25% of the procedures.

Table 18: Statistics on expected and actual blood loss by severity of surgical procedure (PSURG)

Severity of Procedure / Parameter[2]		Statistics on Blood Loss							
		n[1]	Mean	SD	Min	Q1	Median	Q3	Max
Minor	Average Expected Blood Loss (mL)	9	6.11	3.333	0.0	5.00	5.00	10.00	10.0
	Maximal Expected Blood Loss (mL)	9	12.78	8.700	0.0	10.00	10.00	15.00	30.0
	Actual Blood Loss (mL)	8	2.25	3.655	0.0	0.00	0.00	4.00	10.0
Major	Expected Blood Loss Perioperative (mL)	1	5.00	--	5.0	5.00	5.00	5.00	5.0
	Actual Blood Loss Perioperative (mL)	1	5.00	--	5.0	5.00	5.00	5.00	5.0
	Expected Blood Loss Postoperative (mL)	1	0.00	--	0.0	0.00	0.00	0.00	0.0
	Actual Blood Loss Postoperative (mL)	1	0.00	--	0.0	0.00	0.00	0.00	0.0
	Average Expected Blood Loss (mL)	16	71.38	107.329	2.0	7.50	40.00	50.00	400.0
	Maximal Expected Blood Loss (mL)	16	203.44	264.970	5.0	40.00	100.00	225.00	1000.0
	Actual Blood Loss (mL)	16	51.56	76.457	0.0	5.00	22.50	47.50	260.0
Total	Expected Blood Loss Perioperative (mL)	1	5.00	--	5.0	5.00	5.00	5.00	5.0
	Actual Blood Loss Perioperative (mL)	1	5.00	--	5.0	5.00	5.00	5.00	5.0
	Expected Blood Loss Postoperative (mL)	1	0.00	--	0.0	0.00	0.00	0.00	0.0
	Actual Blood Loss Postoperative (mL)	1	0.00	--	0.0	0.00	0.00	0.00	0.0
	Average Expected Blood Loss (mL)	25	47.88	90.696	0.0	5.00	10.00	50.00	400.0
	Maximal Expected Blood Loss (mL)	25	134.80	229.413	0.0	10.00	40.00	200.00	1000.0
	Actual Blood Loss (mL)	24	35.13	66.184	0.0	0.00	7.50	32.50	260.0

[1] Number of surgical procedures treated with *Nuwiq®* prior to surgery with available data on blood loss
[2] For blood loss parameter collected in individual studies, Table 14.2.4-6
min, max = minimum, maximum; PSURG = pooled surgery set; Q1, Q3 = interquartile range; SD = standard deviation
Source: Table 14.2.4-7

6.3. Discussion

GENA-99: Overall, no major concerns arise from the study data. 78 HA patients (10 moderate, 68 severe) were treated with Nuwiq (median age at enrolment was 10 years, 10 patients had a history of FVIII inhibitor). Of note, the study was planned to collect data on 200 PTPs. 77 patients received prophylactic treatment, 1 patients received on-demand only, and one patient switched between treatment regimens. Mean prophylactic treatment duration was 42.7 weeks (median 24.3 weeks) and patients received a mean of 113.6 infusions for any reason (median 110 infusions). Of 64 patients who completed the study, 61 patients had ≥ 100 EDs. Average dose exposure was 39.5 IU/kg per ED or 38.7 IU/kg per infusion.

Prophylactic efficacy was tested on the basis of bleeding frequencies, i.e. ABR. 252 BEs occurred in 74 patients with at least 3 months prophylactic treatment. Mean ABR for all bleeds was 4.09 (SD 6.47, median 2.39 with IQR 0-4.87 and full range of 0-38.7). Mean ABR for spontaneous bleeds was 2.09 (SD 4.17, median 0 with IQR 0-2.47 and full range of 0-21). Split by disease severity, the mean total ABR was 5.02 (SD 6.08, median 3.85, range 0-6.04) for moderate haemophilia (N=10 patients), and mean total ABR was 3.94 (SD 6.56, median 2.21, range 0-4.41) for severe haemophilia (N=64). The MAH has noted that the number of patients with moderate haemophilia was overall low and these patients received on average ~ 35% lower amounts of Nuwiq per month. The range of observed bleeding frequencies for patients under prophylactic treatment (up to 38.5 total annualised bleeds and up to 21 annualised spontaneous bleeds) generally appears high. However, the median total ABR observed on-study in patients with at least 3 months under prophylaxis was consistent with the ABR in the 6 months prior to the study: 2.0 (IQR: 0-6, full range 0-36, mean 4.3, SD 6.82). It is acknowledged that ABR measures show notable variability and lack significance in particular in the comparison of prophylactically treated patients.

Efficacy in the on-demand treatment was rated for 246 BEs in 48 prophylactically treated patients. Of these, 217 (88.2%) were treated successfully (i.e. achieved an 'excellent' or 'good' efficacy rating using a four point rating scale). 26 BEs (10.6 %) and 3 BEs (1.2%) achieved an efficacy rating of 'moderate' or 'none' summing up to 29 non-successfully treated BEs (11.8%). Mean and median number of infusions per BE was 1.78 (SD 2.02) and 1.0 (IQR: 1.00, 2.00; range: 1-24), respectively. Median dose per infusion per BE was 35.65 IU/kg (IQR: 27.78, 42.64; range: 14.0-76.1). In sum, on-demand efficacy data do not raise major concerns and generally align with initial MA data of Nuwiq. However, there were three non-responding patients (one patient that was treated with 24 infusions) and reasons for the numerical high range of injections per bleeding episode (1-24) and EDs (1-17) remain unclear.

Efficacy in GENA-99 was also evaluated during surgical prophylaxis. These data raise some concerns on which basis the excellent efficacy ratings have been achieved. 3 out of 5 rated procedures are missing data for actual vs. expected blood loss. Two rated procedures where a minor surgery of port removal, one with reinsertion with post-op 9 infusions whereas in the other procedure only 2 post-op infusion were administered. Additionally, one patient with major surgery (right knee synovectomy) with only subtle actual blood loss of 5ml had 11 Nuwiq infusions post-op.

Integrated analysis: Treatment success rates for BE occurring under prophylactic treatment were 92.1% for minor, 78.7% for moderate to major, and 57.5% for major to life-threatening bleeds (overall treatment success was 84.3%). These data partly align with those reported in the Nuwiq EPAR (EMA/CHMP/279301/2014). E.g. among the pivotal studies, treatment success (i.e. those with an 'excellent' or 'good' rating) for minor bleeds was 98.6% in GENA-01, 100% in GENA-08, and 98.4% in GENA-03 study. For moderate to major bleeds, success rates were 91.7% (GENA-01), 100% (GENA-08), and 60.9% (GENA-03). GENA-03 was a paediatric study in patients ≤12 years where 50% achieved an 'excellent' rating, and 10.9% a 'good' rating. No valid comparison can be made with

regard to major to life threatening bleeds for which treatment success was 66.7% according to the EPAR, but this numbers was based on three bleeds only (for comparison: integrated analysis 57.5% treatment success for major to life threatening bleeds with N=23). Therefore, treatment efficacy at least for moderate to major bleeds appears to be somewhat lower in the integrated GENA-pool analysis, however, clinical significance is unclear. For surgical prophylaxis in the GENA-pool, 31 patients underwent 51 surgeries that were treated with Nuwiq. 21 surgeries were major, 15 minor, and 15 had unknown severity. Actual range of blood loss was 0.0-260.0 mL (median: 7.5 mL, Q3: 32.50 mL, data available for n=25 procedures, mean blood loss was 35.13 mL with n=24). Treatment success was unknown for 5-8 procedures (depending on the rating procedure, i.e. surgeon intraoperative, surgeon postoperative, haematologist postoperative). Treatment success intraoperative (n=24) was 75% (25% unknown), and postoperative 74.2-86.1% (unknown 13.9-25.0%). There was no procedure rated non-successful. The mean total number of injections (preoperative, at surgery day, intraoperative, postoperative) was 13 injections (and 8.3 EDs), with the majority administered postoperatively. Taking into account the heterogeneity in surgical procedures, dosing & consumption data, and success evaluations, the data for surgical prophylaxis are considered acceptable. However, there are some concerns on the maximum number of postoperatively administered injections (max: 75.0, median 9.5, Q3: 14) with a maximum of 53 EDs, i.e. in 25% of the surgical procedures 14-75 injections have been administered postoperatively.

Overall, a total of 216 HA patients (208 with severe HA), prophylactically treated with Nuwiq for ≥100 EDs, have been evaluated for efficacy (prophylactic efficacy, on-demand treatment of breakthrough bleeds, surgical prophylaxis) and safety to meet the requirements of the EMA FVIII Guideline. Patient characteristics are balanced among age, body weight, race/ethnicity, and geographical location of study sites. No major concerns arise from the submitted efficacy data yet a substantial number of issues has been identified in almost all domains of the efficacy evaluation. In GENA-99 study, there was a numerical high range of injections per BEs with up to 24 injections or 17 EDs. As for the total GENA-pool, it appears that a considerable portion of adult as well as paediatric subjects received higher than the recommended usual prophylactic dosing. Patients in one study showed notable higher annualized bleeding rates (GENA-21b) when compared to other studies included in the integrated analysis and treatment success for BE, in particular for major to life-threatening bleeds, falls short on the data currently reported in the Nuwiq EPAR. To rule out or minimise uncertainties about low efficacy, additional information have to be submitted.

7. Clinical Safety aspects

7.1. Methods – analysis of data submitted

See 8.1.

7.2. Results

Immunogenicity and Safety Results - Gena-99

In this study, testing for FVIII inhibitors could be carried out at any time at the physician's discretion. Furthermore, at each visit, patients were checked for clinical symptoms suggesting FVIII inhibitor development and any suspicion of inhibitor formation was to be investigated by FVIII inhibitor testing. Before patient inclusion into the study, and as recommended in the Guideline EMA/CHMP/BPWP/144533/2009, there was to be no clinical suspicion of FVIII inhibitors. A recovery and inhibitor test could have been performed to confirm that the patient was negative at study entry. In the event of a positive test, it was recommended to test a second separately drawn sample.

FVIII inhibitor status testing was performed for 40 patients (51.3%) at baseline, for 44 patients (56.4%) between screening and completion, and 21 patients (26.9%) at study completion. No FVIII inhibitors were detected and no clinical symptoms led to suspicion of inhibitor formation in any patient treated. It should be noted that around one third of patients completed the study during the COVID-19 pandemic and many of these patients had remote visits with no testing for FVIII inhibitors at study completion.

Table 14.3.1-2
Factor VIII inhibitor status at screening (baseline), between screening and completion and at completion
(All subjects included in the safety set (SAF), N=78)

Age Class / Result		Screening (Baseline)		Between Screening and Completion[2]		Completion (Last Visit)	
		N	%	N	%	N	%
< 12 Years	Negative[1]	20	50.0	24	60.0	11	27.5
	Not Done	20	50.0	16	40.0	29	72.5
	Positive	0	0.0	0	0.0	0	0.0
	Total	40	100.0	40	100.0	40	100.0
12 - < 18 Years	Negative[1]	5	41.7	6	50.0	3	25.0
	Not Done	7	58.3	6	50.0	9	75.0
	Positive	0	0.0	0	0.0	0	0.0
	Total	12	100.0	12	100.0	12	100.0
>=18 Years	Negative[1]	15	57.7	14	53.8	7	26.9
	Not Done	11	42.3	12	46.2	19	73.1
	Positive	0	0.0	0	0.0	0	0.0
	Total	26	100.0	26	100.0	26	100.0
Total	Negative[1]	40	51.3	44	56.4	21	26.9
	Not Done	38	48.7	34	43.6	57	73.1
	Positive	0	0.0	0	0.0	0	0.0
	Total	78	100.0	78	100.0	78	100.0

***Assessor's comment*:** The inhibitor testing procedures appear not to be in line with the EMA/CHMP/BPWP/144533/2009 guideline. For post-marketing investigation, a recovery and inhibitor test in a central laboratory should confirm that the patient is inhibitor negative at study entry. The

inhibitor testing schedule foresees inhibitor and recovery testing at ED10-15, ED50-75, and at ED~100. It remains unclear why not all subjects have been tested accordingly (taken into account those who could not be tested due to COVID-19 pandemic). Apparently only half of the patients have been tested at entry and during the study, and only a quarter at study end. A detailed explanation is requested by the MAH. The MAH should also provide an outline or graphical presentation detailing time points and frequency of testing for individual patients.

No hypersensitivity reactions or thromboembolic events occurred during the study. No ADRs were observed during the study.

One death was recorded in the study. The patient was reported as having died due to a possible intentional/unintentional overdose of anti-depressant prescribed medications. The investigator reported no suspected relationship between Nuwiq and the death of the patient and the event was deemed unrelated to Nuwiq.

Long-term Safety and Immunogenicity – Integrated Analysis

A total of 12 ADRs were experienced by 8 patients, giving a subject-related incidence of 3.7% and an incidence rate per year of 0.036. The ADRs were 5 events of pyrexia in 4 patients (incidence 1.85%), 3 events of dizziness in 2 patients (incidence 0.93%), and single events of dyspnoea, headache, malaise, and chest pain (incidence 0.46% for each). Only 1 ADR (mild pyrexia requiring hospitalisation) was assessed as serious; none led to death or discontinuation. No hypersensitivity reactions or thromboembolic events occurred.

Assessor's comments:

- Apparently, one patient experienced a total of 5 ADRs (3x dizziness, 1x malaise, 1x chest pain). The MAH is asked to provide additional clarification for this accumulation of ADRs and to comment on any potential predisposing medical history.

- Tightness of the chest is described SmPC and the package leaflet as possible side effect (Sections 4.4. and 4.8 of Annex I, Section 4 of Annex III). As from the integrated analysis, the ADR of chest pain (possible causality, mild severity, outcome: recovered/resolved) is not included in the tabulated list of adverse reactions if the current SmPC. Clarification is requested.

No patient in the GENA-POOL tested positive for FVIII inhibitors, and no clinical symptoms led to suspicion of inhibitor formation in any patient in the GENA-POOL. FVIII inhibitor testing was not done for 53 patients at screening, 62 patients between screening and completion, and 65 patients at study completion; the majority of these patients were in the non-interventional studies GENA-99 and GENA-100 (48, 35, 60 patients, respectively) in which FVIII inhibitor testing at set timepoints was not required.

Assessor's comment: The MAH is requested to outline, how many subjects finally had been scheduled for inhibitor testing and how many finally have been tested according to the schedule outlined in the clinical FVIII Guideline.

7.3. Discussion

In the GENA-99 study, FVIII inhibitor status testing was performed for 40 patients (51.3%) at baseline, for 44 patients (56.4%) between screening and completion, and 21 patients (26.9%) at study completion. No FVIII inhibitors were detected and no clinical symptoms led to suspicion of inhibitor formation in any patient treated. It was noted that around one third of patients completed the study during the COVID-19 pandemic and many of these patients had remote visits with no testing for FVIII inhibitors at study completion. No ADRs including hypersensitivity reactions and thromboembolic events were observed during the study. One death was recorded during the study which was considered unrelated to Nuwiq treatment but was suspected to overdose of multiple medications on the medical background of an ongoing post-traumatic stress disorder and depression. Although these safety results do not raise concerns, there are concerns related to the study procedures. Among 78 patients, inhibitor testing was not done for 38 (48.7%) at screening, 34 (43.6%) between screening and completion, and 57 (73.1%) at completion. While it is acknowledged that inhibitor testing at study completion could have been hampered (only 26.9% of patients was tested) by the pandemic situation in 2020 (Last Patient Out: 20-Aug-2020), it remains generally unclear why the inhibitor testing procedures were not in line with the FVIII guideline and whether inconsistent testing procedures may have affected immunogenicity results.

From the integrated analysis, overall no safety signals have been identified. However, the description of inhibitor testing procedures lacks clarity (i.e. it is described for how many patients inhibitor testing was not done at distinct time point/periods) and it is unknown how many patients have been tested in accordance with the testing scheme outlined in the FVIII Guideline. In addition, there is a lack of description regarding the accumulation of 5 ADRs in a single subject.

Overall, no safety signals are identified but presented data are compromised by inhibitor testing procedures appearing not aligned with the FVIII guideline. Further information accompanied by an appropriate expert statement on data validity are requested.

7.4. Direct Healthcare Professional Communication

N/A

8. PRAC advice

N/A

9. Request for supplementary information

9.1. Major objections

None.

9.2. Other concerns

Clinical aspects

1) The goal of study GENA-99 was to collect data in 200 PTPs with HA (FVIII:C ≤2%). The study was completed in 2021, with data obtained from 78 patients. The MAH has stated that in agreement with EMA in 2018, patient data from other post-authorisation studies will contribute to the goal of documenting the long-term safety of treatment with Nuwiq in 200 PTPs. However, no reference regarding this agreement has been made. The MAH is asked for clarification.
2) The MAH is requested to further clarify the numerical high range of injections per treatment-emergent bleeding episode (1-24) and EDs (1-17) in study GENA-99. A detailed narrative of the three non-responding patients, in particular of the patient treated with 24 infusions, should be provided along with a critical expert statement.
3) Additional explanation is requested for the surgical efficacy ratings in study GENA-99. For 3/5 rated procedures data for actual vs. expected blood loss are not available. Two rated procedures where a minor surgery of port removal, one with reinsertion with post-op 9 infusions whereas the other patient received only 2 infusion post-op. Additionally, one patient with right knee synovectomy (a major surgery) with actual blood loss of 5 ml had 11 infusions of Nuwiq post-op. It is thus unclear on which basis excellent ratings could have been achieved.
4) The inhibitor testing procedures in study GENA-99 appear not to be in line with the EMA/CHMP/BPWP/144533/2009 guideline. For post-marketing investigation, a recovery and inhibitor test in a central laboratory should confirm that the patient is inhibitor negative at study entry. The inhibitor testing schedule foresees inhibitor and recovery testing at ED10-15, ED50-75, and at ED~100. It remains unclear why not all subjects have been tested accordingly (taken into account those who could not be tested due to COVID-19 pandemic). Apparently only half of the patients have been tested at entry and during the study, and only a quarter at study end. A detailed explanation is requested by the MAH. The MAH should also provide an outline or graphical presentation detailing time points and frequency of testing for individual patients and it should be highlighted how many patients have been tested in accordance with the guideline.
5) For the complete GENA-pool including all age groups (N=216), median prophylactic dosing per injection was 35.41 IU/kg (third quartile Q3: 43.41 IU/kg, max: 101.9 IU/kg) and per ED 35.41 IU/kg (Q3: 43.52 IU/kg, max: 103 IU/kg). For the age class ≥ 18 years (N=76), median prophylactic dosing per injection was 35.17 IU/kg (Q3: 42.55 IU/kg; max: 85.4 IU/kg). For the age class <12 years (N=123), median prophylactic dosing per injection was 36.33 IU/kg (Q3: 44.12 IU/kg; max: 101.9 IU/kg). Data are derived from Table 14.2.3.1-1 of the study report. It appears that a considerable portion, i.e. about a quarter of the patients (adults as well as paediatrics), received higher than the recommended usual prophylactic dosing (20 to 40 IU/kg) with maximum 2-fold of the recommended prophylactic dosing. A detailed clarification is requested.
6) Although ABR estimates generally lack sensitivity when it comes to the comparison of prophylactically treated patients, among the individual studies in the GENA-pool, the GENA-21b

study showed notable higher ABR frequencies. The MAH is asked to provide a possible explanation for this observation.

7) In the integrated analysis, treatment success rates for BE occurring under prophylactic treatment were 92.1% for minor, 78.7% for moderate to major, and 57.5% for major to life-threatening bleeds (overall treatment success was 84.3%). These data just partly align with those reported in the Nuwiq EPAR (EMA/CHMP/279301/2014). E.g. for moderate to major bleeds among the pivotal studies treatment success rates were 91.7% (GENA-01), 100% (GENA-08), and 60.9% (GENA-03). Thus, treatment efficacy for moderate to major bleeds appears to be somewhat lower in the integrated GENA-pool analysis. The MAH should comment on the clinical significance of this observation.
8) For the 51 surgeries in the integrated analysis, there was a mean total (preoperative, at surgery day, intraoperative, postoperative) number of 13 injections and 8.3 EDs, with the majority in the postoperative stage. The maximum number of postoperative injections was 75.0 (median 9.5, Q3: 14) with a maximum of 53 EDs (median: 6.00, Q3: 9.00). I.e. in 25% of the surgical procedures 14-75 injections have been administered postoperatively. This range appears unusual high and the MAH is requested for clarification.
9) Integrated Safety Analysis
    a. Apparently, one patient (GENA-21/ GENA-21B) experienced a total of 5 ADRs (3x dizziness, 1x malaise, 1x chest pain). The MAH is asked to provide additional clarification for this accumulation of ADRs and to comment on any potential predisposing medical history.
    b. Tightness of the chest is described SmPC and the package leaflet as possible side effect (Sections 4.4. and 4.8 of Annex I, Section 4 of Annex III). As from the integrated analysis, the ADR of chest pain (possible causality, mild severity, outcome: recovered/resolved) is not included in the tabulated list of adverse reactions of the current SmPC. Clarification is requested.
    c. Study procedures for FVIII inhibitor testing appear to be decoupled from the requirements set out in the FVIII guideline. The MAH is requested to outline how many subjects had been scheduled for inhibitor testing and how many finally have been tested according to the schedule outlined in the FVIII Guideline. Clarifications should be accompanied by an expert statement on data validity.

10. Assessment of the responses to the request for supplementary information

10.1. Other concerns

Clinical aspects

Question 1

The goal of study GENA-99 was to collect data in 200 PTPs with HA (FVIII:C ≤2%). The study was completed in 2021, with data obtained from 78 patients. The MAH has stated that in agreement with EMA in 2018, patient data from other post-authorisation studies will contribute to the goal of documenting the long-term safety of treatment with Nuwiq in 200 PTPs. However, no reference regarding this agreement has been made. The MAH is asked for clarification.

Summary of the WSA's response

In the Final Assessment Report for the Post-Authorisation Measure Vihuma 004.1, Nuwiq 004.2, dated 23 March 2018 (in the report which was attached to the responses), the assessor commented: "It is considered acceptable to include data from patients participating in post-marketing interventional studies, providing that the protocol for the GENA-99 is followed with regards to eligibility criteria and outcome parameters, and maintaining the proportions of patients as specified in the protocol with regards to age distribution and severity of disease".
This was confirmed again by the assessor in the Final Assessment Report for the Post-Authorisation Measure MEA 004.3 and 004.2 dated 28 August 2018 (in the report which was attached to the responses).

Assessment of the WSA's response

As from the referenced documents, the MAH was requested to discuss the low inclusion rate of study GENA-99. It was stated by the MAH that the low inclusion rate was due to strong competition in the haemophilia A market and difficulties to recruit participating centres due to reluctance to participate in post-marketing studies as well as regulatory difficulties on a national level. CHMP accepted to include data from patients participating in post-marketing interventional studies, provided that the protocol for the GENA -99 would be adhered to with regards to eligibility criteria and outcome parameters.

The MAH's submissions are therefore considered acceptable in respect to data compensation subsequent the low recruitment rate of the GENA-99 study.

Conclusion

Issue resolved.

Question 2

The MAH is requested to further clarify the numerical high range of injections per treatment-emergent bleeding episode (1-24) and EDs (1-17) in study GENA-99. A detailed narrative of the three non-responding patients, in particular of one patient treated with 24 infusions, should be provided along with a critical expert statement.

Summary of the WSA's response

The MAH would like to clarify that there were not "three non-responding patients" but three bleeding episodes (BE) in three patients for which treatment efficacy was assessed as "none".

Overall, the percentage of "none" assessments in GENA-99 was 1.2% and thus was comparable to adults undergoing prophylactic treatment with Nuwiq: GENA-08 (0.0%), GENA-21 (1.7%), GENA-21b (1.4%).

The 3 patients in study GENA-99 that received a numerical high number of infusions and where 3 BEs were rated as none are discussed below.

Patient 1

This patient was on Nuwiq for 3 years and was enrolled in GENA-99. He experienced in total 5 BEs of moderate to major intensity and only one efficacy assessment was rated none, for an elbow bleed which required 10 infusions (9 with 25.97 IU/kg and 1 with 51.95 IU/kg) and lasted 7 days. The dose to treat this BE may have been sub-optimal to treat a moderate to major BE (30-60 IU/kg are recommended in SmPC). All other moderate to major BEs were rated with either good or moderate efficacy and were treated with higher doses according to the SmPC (38.46-51.28 IU/kg). The efficacy of the left elbow bleed was originally assessed as "good" by the patient/investigator but following a query from the MAH it was changed to "none" based on the bleeding efficacy criteria in the patient diary. It should be noted that the efficacy of two other moderate to major BEs which were treated with 3 infusions (and lasted 3 days) was initially assessed as "good" and subsequently changed to "moderate" following a query by the MAH as per the definition of the efficacy assessment criterion for moderate. He completed the study according to protocol with 182 EDs with no suspicion of inhibitor while he was on the study.

Patient 2

This patient with moderate haemophilia was on Nuwiq for 4 years and was enrolled in GENA-99. He experienced a total of 19 BEs during the course of the study, all spontaneous bleeds in his left knee (indicating a target joint). Twelve of the BEs were of moderate to major intensity, 10 of which were treated with 1 or 2 infusions and the efficacy was rated as excellent (n=6) and good (n=4).

The last moderate to major BE was treated with 4 infusions of Nuwiq, was ongoing at the time of the completion visit and treatment was rated as "none". The site informed the MAH that the patient treated the bleeding until1 day after study completion and resumed his prophylaxis with Nuwiq 4 days later.. The patient completed the study according to protocol, with 183 EDs with no suspicion of inhibitor formation.

Patient 3

This patient participated in study GENA-21, thereafter continued prophylaxis with Nuwiq and was enrolled in GENA-99 2 years later. In GENA-21 he experienced one moderate to major BE which required 1 infusion and the efficacy was rated as excellent.

In the GENA-99 study the patient experienced 2 BEs. The moderate to major spontaneous BE in the left knee was treated with 24 infusions of Nuwiq (11 with 65.6 IU/kg, 8 with 32.8 IU/kg, 2 with 49.13 IU/kg, 2 with 16.4 IU/kg, and 1 with 24.6 IU/kg). The site reported: "It was a target joint left knee where he had sub clinical bleed. It needed 14 doses of Nuwiq to treat to improve the bleed, but he continued to bleed into the joint on the slightest exertion." The patient tested negative for FVIII

inhibitors at the end of this BE. He discontinued the study prematurely at his own request with a total of 34 EDs.

Assessment of the WSA's response

The MAH provided additional information for three patients which each had one bleeding episodes for which treatment efficacy was assessed as none. Individual reasons for the none-effective ratings (one BE was sub-optimally treated and two cases were target joint bleeds) are acknowledged and data indicate that these patients generally responded to Nuwiq treatment of other bleeding episodes. Therefore, it is endorsed that these cases are consistent with the favourable efficacy profile of Nuwiq.

Conclusion

Issue resolved.

Question 3

Additional explanation is requested for the surgical efficacy ratings in study GENA-99. For 3/5 rated procedures data for actual vs. expected blood loss are not available. Two rated procedures where a minor surgery of port removal, one with reinsertion with post-op 9 infusions whereas the other patient received only 2 infusions post-op. Additionally, one patient with right knee synovectomy a major surgery with actual blood loss of 5 ml had 11 infusions of Nuwiq post-op. It is thus unclear on which basis excellent ratings could have been achieved.

Summary of the WSA's response

Surgical efficacy ratings in GENA-99 were done by the surgeon/haematologist based on their clinical judgement, which took into account the blood loss during and after surgery as well as the occurrence of post-surgical bleeding.

The number of post-operative infusions or the duration of post-operative treatment were not taken into consideration for the efficacy assessment. The decision as to how long patients were to be treated post-surgery was up to a sites' standard of care and the clinical disposition of the patient.

As per SmPC, for major surgery the treatment recommendation is as follow: Repeat infusion every 8–24 hours until adequate wound healing (Factor VIII activity required 80–100% [pre- and postoperative]), then therapy for at least another 7 days to maintain a factor VIII activity of 30% to 60% (IU/dL). Considering the treatment recommendations in the SmPC, the postoperative treatment in the surgeries in GENA-99 study did not deviate from those recommendations.

In one patient the port removal and reinsertion, which was classified as minor, required 9 post-surgical infusions due to an infected port potentially delaying wound healing.

As per communication with the site the following was confirmed: "only a couple of additional days of treatment may be needed while for a more complex port removal and reinsertion (e.g. an infected port, the usual treatment is 3 days of 3-4 doses per day, then decreasing to 2 days of 2 doses per day then daily until patients return to regular prophylaxis".

No actual versus expected blood loss data were provided for 3 surgeries in 3 patients which are described in more detail below:

Two of those procedures were port removal and port insertion procedures in2 patients, with post-operative treatment of 0 infusions and 2 infusions, respectively. In both cases no bleeding was reported after surgery. One patient resumed routine prophylactic infusions after the surgery and the other patient resumed prophylaxis after 2 post-surgery infusions.

In comparison, port insertion and port removal procedures also occurred in studies GENA-03 and GENA-05. In these studies, the expected average blood loss was between 0 and 50 mL and actual blood loss was between 0 and 30 mL, with the number of post-operative infusions to prevent bleeding ranging from 3 to 30. The majority of these procedures were rated as excellent and were considered to be successful.

The 3rd procedure for which data on expected average and actual blood loss were not available is a hip prosthesis the patient was treated with 11 infusions / 8 EDs post-surgery to prevent bleeding. This treatment is also in line with the SmPC. No bleeding during or after surgery was reported.

Similar surgeries were performed both in pivotal study GENA-08 (expected blood loss 500 mL, actual blood loss 0 mL, 15 post-operative infusions) and in interventional study GENA-21b (expected blood loss 400 mL, actual blood loss 260 mL, 20 post-operative infusions). The efficacy assessment for both surgeries was excellent.

In conclusion, prevention of post-surgical bleeding and not the number of post-surgical infusions is the decisive factor in successful peri-operative prophylaxis in haemophilia patients. In study GENA-99, no complications during surgery and no post-operative bleedings were reported for these 3 patients, justifying the excellent rating by the investigators in this study.

Assessment of the WSA's response

The MAH further clarified the assessment of the surgical efficacy ratings, in particular that number of post-operative infusions and the duration of post-operative treatment were not accounted for. It is acknowledged that the surgical procedures have been treated in line with SmPC recommendations and that the efficacy assessment was based on individual clinical judgement rather than predefined criteria. Further details on the procedures and comparative efficacy data of other Nuwiq studies suggest that surgical efficacy in GENA-99 study was at least in accordance with preceding results. The MAH's submissions on this matter are therefore accepted.

Conclusion

Issue resolved.

Question 4

The inhibitor testing procedures in study GENA-99 appear not to be in line with the EMA/CHMP/BPWP/144533/2009 guideline. For post-marketing investigation, a recovery and inhibitor test in a central laboratory should confirm that the patient is inhibitor negative at study entry. The inhibitor testing schedule foresees inhibitor and recovery testing at ED10-15, ED50-75, and at ED~100. It remains unclear why not all subjects have been tested accordingly (taken into account those who could not be tested due to COVID-19 pandemic). Apparently only half of the patients have

been tested at entry and during the study, and only a quarter at study end. A detailed explanation is requested by the MAH. The MAH should also provide an outline or graphical presentation detailing time points and frequency of testing for individual patients and it should be highlighted how many patients have been tested in accordance with the guideline.

Summary of the WSA's response

The MAH is aware of the EMA/CHMP/BPWP/144533/2009 guideline and implemented a testing schedule for inhibitors (using a central lab) and *in-vivo*-recovery into the GENA-99 protocol. However, this schedule differs significantly from routine clinical practice, and thus the testing schedule could not be enforced but only recommended in GENA-99, which was designed as a non-interventional study. In routine clinical practice inhibitor testing is performed less frequently [1] and testing was done according to the local standard of care. Inhibitor testing is usually infrequent for previously treated patients (PTPs) if there are no clinical symptoms that indicate inhibitory activity, such as frequent bleeds under prophylaxis or ineffective treatment of BEs. The World Federation of Hemophilia (WFH) for example recommends inhibitor testing in PTPs to be performed once every 12 months [2], using local laboratories. In addition, the study design which included the use of a central laboratory posed problems for a non-interventional study. The MAH reported the difficulties in implementing the above-mentioned guidelines to EMA in 2018; (Responses to List of Questions in final AR dated 14 December 2017 (PAM MEA 004/004.01), Nuwiq sequence 63/ Vihuma sequence 12) this was submitted on 01 February 2018 and was acknowledged by the assessor in their response. In fact, in order to conduct study GENA-99 in France, the MAH had to issue an amended protocol to remove all interventional aspects of the study in order to receive approval from the authorities.

The MAH would like to point out that, according to the protocol, the outcome parameter for assessing immunogenicity of Nuwiq was the incidence of FVIII inhibitors with the diagnosis based on clinical observation and confirmed by FVIII inhibitor testing in the laboratory. No clinical symptoms led to suspicion of inhibitor formation in any patient treated with Nuwiq in the study GENA-99 which would in turn justify inhibitor testing in the routine care of the patients enrolled in this study. Whether or not a suspicion of inhibitor formation is present was actively asked for each patient visit and recorded in the CRF.

In total 122 inhibitor tests were performed in study GENA-99, in 62/78 patients. The total number of inhibitor tests performed per time point are presented in Table 4.

Table 4: Total Number of Inhibitor Tests Per Visit Schedule in GENA-99

Time points	Total number of tests per time point / Number of patients tested per time point
Screening	40 / 40
ED 10-15	8 / 8
ED 50-75	17 / 17
ED≥100	19 / 19
Other timepoints between screening and ED 100	38 / 36

Of note, out of 16 patients who did not have any inhibitor testing while on the study, 14 were from EU

member states. The reason why the inhibitor test could not be performed is listed in List 16.2.8-3 for each visit. Covid-19 affected inhibitor testing for 7 patients that were scheduled to be tested between ED50-75 and 4 patients at ED~100 (List 16.2.8-3). These tests could not be performed.

In conclusion, the guideline deviates from standard practice and mandated blood draws at defined timepoints with central laboratory testing posed obstacles for ethics committee approvals in France and the UK, both member states of EMA at the time (see also Responses to List of Questions in final AR dated 14 December 2017 (PAM MEA 004/004.01), Nuwiq sequence 63/ Vihuma sequence 12). In order for the study to be approved by ethics committees, inhibitor testing had to be performed per the sites standard practice. Clinical symptoms for inhibitory activity were monitored during the study.

Furthermore, the MAH has provided data showing the safety of Nuwiq. As neither suspicion of inhibitor nor other ADRs such as hypersensitivity reactions or thromboembolic events were reported during the observational period, the favourable safety profile of Nuwiq as previously shown in pivotal studies was confirmed. Please also refer to the critical expert statement attached in section 2.5.

[1] Manuel Carcao, Jenny Goudemand, Treatment of Hemophilia INHIBITORS IN HEMOPHILIA: A PRIMER, Fifth Edition, November 2018, No. 7

[2] The WFH guidelines for the management of hemophilia, 3rd Edition: Document: TG Resource Hub One-Pager: Chapter 8_Recommendations_Inhibitors to Clotting Factor (wfh.org)

Assessment of the WSA's response

It is acknowledged that due to the non-interventional study design and definition of the safety outcome the inhibitor testing procedures in GENA-99 study deviate from recommendations made in the EMA FVIII Guideline. Consequently, only a minority of patients have been tested for FVIII inhibitory antibodies at any time point. This compromises the validity of the submitted immunogenicity data.
As from the critical expert statement, the MAH confirmed that "all patients were monitored for clinical symptoms leading to suspicion of inhibitor formation, with the investigator documenting yes or no for the presence of such symptoms at each visit. Any patients with such symptoms were to be followed-up with laboratory tests for inhibitor formation. No patient in study GENA-99 presented with clinical symptoms that led to suspicion of inhibitor formation according to the investigators".
Considering the study design and the primary outcome definition, it is acknowledged that study results generally could reflect an expectable low inhibitor incidence in PTPs.

Conclusion

Issue not further pursued.

Please also refer to Question 9.

Question 5

For the complete GENA-pool including all age groups (N=216), median prophylactic dosing per injection was 35.41 IU/kg (third quartile Q3: 43.41 IU/kg, max: 101.9 IU/kg) and per ED 35.41 IU/kg (Q3: 43.52 IU/kg, max: 103 IU/kg). For the age class ≥ 18 years (N=76), median prophylactic dosing per injection was 35.17 IU/kg (Q3: 42.55 IU/kg; max: 85.4 IU/kg). For the age class <12 years (N=123), median prophylactic dosing per injection was 36.33 IU/kg (Q3: 44.12 IU/kg; max: 101.9 IU/kg). Data are derived from Table 14.2.3.1-1 of the study report. It appears that a considerable portion, i.e. about a quarter of the patients (adults as well as paediatrics), received higher than the

recommended usual prophylactic dosing (20 to 40 IU/kg) with maximum 2-fold of the recommended prophylactic dosing. A detailed clarification is requested.

Summary of the WSA's response

Appendix 2 submitted as part of the response shows that 61 patients (28.2%) of the 216 patients from the GENA-pool received an average prophylactic dose of more than 41 IU/kg. These 61 patients participated in studies GENA-15, GENA-21, GENA-21b, and GENA-100.

The majority of these patients (N=42) fall into the age class <12 years (study GENA-15, GENA-13, GENA-99, and GENA-100). Twenty-eight of those patients under the age of 12 received a dose between 41 and 50 IU/kg and 14 received a dose ⩾50 IU/kg. Deviations from the recommended dose range were generally due to the low body weight of some patients and the instruction to use entire vial contents in interventional studies.

In studies GENA-21 and GENA-21b, which enrolled patients ⩾ 18 years, the allowed dose range was up to 80 IU/kg and up to 65 IU/kg, respectively. The goal of these studies was to optimize the dosing based on PK-guided (personalized) prophylaxis.

Single patients in GENA-99 and GENA-100 received higher doses due medical reasons. For example, one patient who underwent synovectomy during the study, had a history of right knee synovitis, a pre-condition that may warrant the treating physician to dose higher, as recommended in the prescribing information.

In study GENA-100, 4 out of 7 patients who were dosed above 41 IU/kg, both children and adults, had several target joints (2-10) requiring treatment with higher doses. One patient had a history of intracranial bleeding that may have necessitated prescription of higher doses.

Of note, the recommendations for long-term prophylaxis in the SmPC indicate that "In some cases, especially in younger patients, shorter dosage intervals and higher doses may be necessary", which is due to the shorter half-life and faster clearance of FVIII in children. It should also be considered that the dosing recommendations for routine prophylaxis with Nuwiq for children differ between countries. For example, while the European SmPC recommends a usual dose of 20-40 IU/kg, the US Prescribing Information recommends a dose of 30 to 50 IU/kg for children between 2 to 11 years.

In conclusion, patients may be prescribed higher doses for various reasons in routine clinical practice.

Assessment of the WSA's response

The MAH admits that there were a large number of patients receiving higher than recommended prophylactic doses. A large proportion of these patients were paediatric which is why higher dosing regimen were applied, with altered PK as the most common underlying reason. Further reasons for higher prophylactic dosing were personalised (PK-based) prophylaxis in adults as well, or individual medical history reasons including presence of target joints, bleedings, or scheduled surgery.

Although the number and extent of higher prophylactic doses are considered noticeable, the MAH's comments on this matter can be accepted.

Conclusion

Issue resolved.

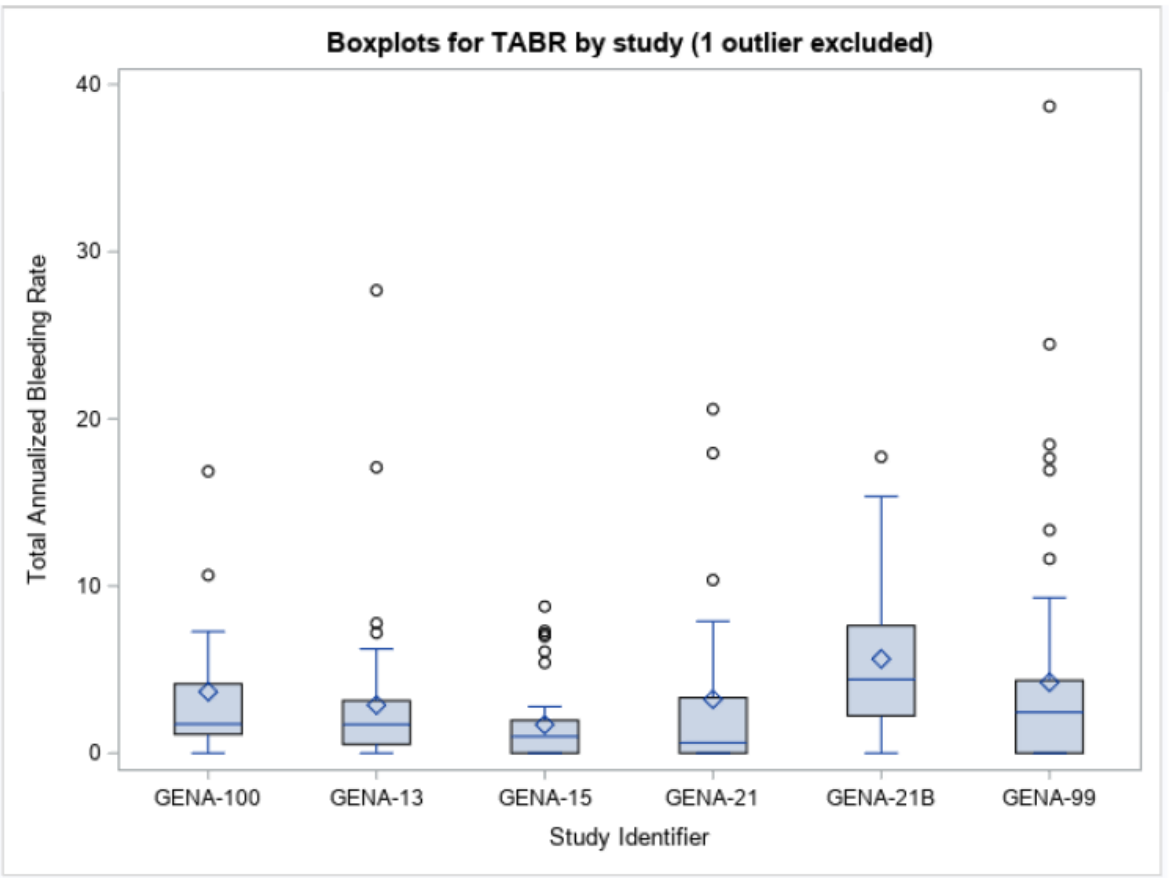
Question 6

Although ABR estimates generally lack sensitivity when it come to the comparison of prophylactically treated patients, among the individual studies in the GENA-pool, the GENA-21b study showed notable higher ABR frequencies. The MAH is asked to provide a possible explanation for this observation.

Summary of the WSA's response

Figure 1 shows the total ABR of the studies included in the GENA-pool.

Figure 1: Boxplots for Total ABR by Study



Source Post-hoc analysis. One outlier (TABR>100) in study GENA-21 has been excluded to obtain a clearer picture of the distributions.

The ABRs appear to be fairly comparable to each other. A post-hoc non-parametric analysis according to Kruskal-Wallis revealed that the differences in the GENA-pool between GENA-21b (study in adults) and paediatric studies GENA-13 and-15 are statistically significant ($p<0.05$), but there is no statistically significant difference between GENA-21b and the other studies (GENA-21, GENA-99, GENA-100) that enrolled adult patients (see Table 5). However, this analysis is limited as it is not the outcome of a prospectively planned analysis, but of a post-hoc analysis.

Table 5: Kruskal-Wallis Analysis of Total ABR

Analysis Variable : TABR Total Annualized Bleeding Rate											
Study Identifier	N Obs	N Miss	Mean	Std Dev	Std Error	Lower 95% CL for Mean	Upper 95% CL for Mean	Median	Minimum	Maximum	Quartile Range
GENA-100	17	0	3.67	4.44	1.08	1.39	5.96	1.74	0.00	16.86	3.02
GENA-13	49	0	2.88	4.63	0.66	1.55	4.21	1.72	0.00	27.68	2.61
GENA-15	39	0	1.71	2.41	0.39	0.92	2.49	1.00	0.00	8.77	1.96
GENA-21	25	0	7.12	20.23	4.05	-1.23	15.47	1.25	0.00	100.54	3.79
GENA-21B	25	0	5.64	4.61	0.92	3.74	7.54	4.41	0.00	17.72	5.39
GENA-99	61	0	4.24	6.81	0.87	2.49	5.98	2.44	0.00	38.69	4.35
GENA-99	61	0	4.24	6.81	0.87	2.49	5.98	2.44	0.00	38.69	4.35

Source: Post-hoc analysis

It is correct that Table 12 of the integrated study report indicates that the median ABR of the 25 patients from GENA-21b in the GENA-99 integrated analysis was 4.41 (also shown in Table 5 above) and thus higher than in the other studies; however, the median ABR of these 25 patients was also higher than the median ABR of 2.04 of all 56 patients included in the entire GENA-21b study (GENA-21b Clinical Study Report). Of note, study GENA-21b enrolled Japanese patients which were not included in any other studies with Nuwiq. The median ABR of the 10 Japanese patients was about 50% higher than those of the entire study population: 3.04 vs 2.04 (GENA-21b Clinical Study Report). The percentage of Japanese patients from GENA-21b included in the GENA-pool analysis was higher than in the entire study (10 of 25 = 40.0% vs 10 of 56 = 17.9%), which may contribute to the relatively high ABR of the GENA-21b patients in the GENA-99-pool analysis. Based on the data available from the Japanese patients in GENA-21b and the full clinical development program, the Japanese authority (PMDA) granted marketing authorisation for Nuwiq in January 2021.

Lastly, when looking at competitor studies with prophylactic treatment, the mean ABR ranged for example from 1.6 (inter quartile range: 0.0, 4.7) for Eloctate [1] to 3.7 (±4.7) for the overall population and 4.0 (±3.4) for the Japanese subpopulation for Adynovate [2].

Considering the range of ABRs reported and median ABRs, the variability of the data, and differing patient populations, the ABRs observed in pivotal study GENA-21b can be considered to be within the range of those reported for other products when used prophylactically. The higher ABRs compared to the other GENA studies can be considered to reflect expected inter-study variability, which has also been observed with other products.

[1] Mahlangu J, Powell JS, Ragni MV, et al. Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. Blood 2014; 123: 317-325

[2] Nogami K, Shima M, Fukutake K, et al. Efficacy and safety of full-length pegylated recombinant factor VIII with extended half-life in previously treated patients with hemophilia A: comparison of data between the general and Japanese study populations. Int J Hematol. 2017 Nov;106(5):704-710.

Assessment of the WSA's response

Post-hoc one-way ANOVA results indicated higher ABRs in adult study GENA-21b when compared to paediatric studies GENA-13 and-15. However, no statistical significance was observed in comparison to ABRs of other studies that enrolled adult patients. The non-significantly higher ABRs in study GENA-21B can be at least partly explained by a differences in the study population. The argumentation can be followed and is acceptable.

Conclusion

Issue resolved.

Question 7

In the integrated analysis, treatment success rates for BE occurring under prophylactic treatment were 92.1% for minor, 78.7% for moderate to major, and 57.5% for major to life-threatening bleeds (overall treatment success was 84.3%). These data just partly align with those reported in the Nuwiq EPAR (EMA/CHMP/279301/2014). E.g. for moderate to major bleeds among the pivotal studies treatment success rates were 91.7% (GENA-01), 100% (GENA-08), and 60.9% (GENA-03). Thus, treatment efficacy for moderate to major bleeds appears to be somewhat lower in the integrated GENA-pool analysis. The MAH should comment on the clinical significance of this observation.

Summary of the WSA's response

The MAH has reviewed the success rate for BEs by age class. Whereas the age distribution in the individual pivotal studies was more homogeneous, the age distribution in the integrated analysis was more diverse with 56.9% of the patients under the age of 12 and an age range between 1 and 71 years.

When comparing efficacy success among the same age class, success rates are aligned between the integrated analysis and the pivotal studies as shown below and are slightly higher in children in the integrated analysis as compared to GENA-03 (Table 6).

Table 6: Success Rate for Treatment of BEs, by Study

Parameter/ Severity of the BE	BE Success (%) / Study				
	GENA-03 (N=32)	Integrated analysis Age class<12- (N=86)	GENA-01 (N=22)	GENA-08 (N= 16)	Integrated analysis Age class>=18 (N=53)
Minor	98.4 (n=60)	92.3 (n=299)	98.6 (n=410)	100 (n=14)	90.4 (n=103)
Moderate to Major	60.9 (n=28)	73.3 (n=162)	91.7 (n=519)	100 (n=14)	87.7 (n=186)
Major to Life threatening	None	87.5 (n=7)	66.7 (n=2)	None	50 (n=16)
Total	82.4 (n=89)	84.5 (n=470)	94.4 (931)	100 (n=28)	85.2 (n=305)

Source: Integrated analysis Table 14.2.2.2.3-5 and Table 14.2.2-1, GENA-01 Table 14.2.25.2 and Table 14.2.35.2, GENA-03 Table 14.2.22.2 and Table 14.2.31.1.1, GENA-08 Table 14.2.12.2 and Table 14.2.7
n= number of BEs; N= Number of patients with treated BE

In conclusion, the success rate of the treatment of moderate to major BEs as well as for all severities was comparable between the pivotal studies GENA-01, GENA-03 and GENA-08 and the integrated analysis, and does not fall short when comparison is made among the same age groups.

Assessment of the WSA's response

The MAH clarified that deviations in the reported treatment success rates of the integrated GENA-pool analysis when compared to individual studies reported in the EPAR result from different age distributions, i.e. in the integrated analysis a larger proportion of paediatric patients <12 years of age was present and which had slightly lower success rates. Age-staggered efficacy data of the integrated

analysis demonstrate that these are in line with success rates of other relevant studies.

Conclusion

Issue resolved.

Question 8

For the 51 surgeries in the integrated analysis, there was a mean total (preoperative, at surgery day, intraoperative, postoperative) number of 13 injections and 8.3 EDs, with the majority in the postoperative stage. The maximum number of postoperative injections was 75.0 (median 9.5, Q3: 14) with a maximum of 53 EDs (median: 6.00, Q3: 9.00). I.e. in 25% of the surgical procedures 14-75 injections have been administered postoperatively. This range appears unusual high and the MAH is requested for clarification.

Summary of the WSA's response

The peri-operative practice in treating Hemophilia A patients' is to infuse prior to the surgery (generally 1 and sometimes 2 infusions) to maintain haemostasis during the surgery. Intra-operative infusions will be given in some cases, if needed. The majority of the infusions are typically given post-surgically (post-surgical prophylaxis) starting after the last suture with the goal to prevent bleeding. The duration and number of infusions of the post-surgical treatment depends on the type and severity of the surgery, and a patient's clinical situation.

Per the SmPC, for major surgery the recommendation is as follows: Repeat infusion every 8–24 hours until adequate wound healing (Factor VIII activity required 80–100% (pre- and postoperative)), then therapy for at least another 7 days to maintain a factor VIII activity of 30% to 60% (IU/dL). Considering the treatment recommendations in the SmPC, the perioperative treatment in GENA studies did not deviate from those recommendations.

Surgeries that required a higher number of post-surgical prophylactic infusions were major surgeries ($\geqslant$20 infusions) and clinical practice may differ from institute to institute and country to country (see Table 7).

Table 7: Surgeries with ≥14 post-operative Nuwiq infusions

Procedure	Severity	Postoperative Infusions
INSERTION OF PORTACATH	Minor	15
T REIMPLANTATION OF THE RIGHT URETHER ACCORDING TO POLITANO-LEADBETHER WITH URETHERAL FOLDING ACCORDING KALIANSKI TECHNIC, II CLOSURE OF METHERO-CUTENEOSTOMY	Major	27
DURING CYSTOSCOPY SMALL SURGICAL PROCEDURE WAS DONE WITH REMOVING OF VEGETATIONS FROM THE BLADDER CLOSE TO RIGHT URETHER ORIFICE	Minor	18
EVACUATION HEMARTHROSIS OF THE LEFT KNEE BY PUNCTURE (INSTALLATION OF SPLINT)	Major	36
PLATE OSTEOSYNTESIS OF LEFT DISTAL TIBIA	Major	42
APPENDECTOMY	Major	75
Left hip joint	Major	20
total knee replacement	Major	44
Synovectomia anterior articulatio tallocruralis lateralis dexter	Major	38
RIGHT KNEE SYNOVECTOMY	Major	22
Knee tep implantation left	Unknown	14
right Knee TEP surgery	Unknown	19

For example, 5 surgeries requiring more than 30 post-surgical prophylactic infusions were looked into in more detail and are described below:

In study GENA-21:

- One major surgery required 75 post-operative infusions (53 EDs): one patient experienced appendicitis. He was hospitalised for an emergency appendectomy and subsequently experienced postoperative wound infection which required extensive treatment. Actual blood loss was 20 mL (10 mL more than the average expected). No wound hematomas were observed. No post-operative bleeding was documented.
- One major surgery required 42 post-operative infusions (21 EDs): one patient underwent plate Osteosynthesis of left distal Tibia. The actual blood loss was 80 mL less than the average expected blood loss. No wound hematomas were observed. No post-operative bleeding was documented.

In study GENA-21b:

- One major surgery required 45 post-operative infusions (36 EDs): one Patient underwent total knee replacement. The average expected and actual blood loss did not differ (Difference=0). One post-surgical bleeding was reported 18 days after the surgery that lasted 4 days and

required 7 infusions.

- One major surgery required 38 post-operative infusions (32 EDs): one patient underwent Synovectomia anterior articulatio tallocruralis lateralis dexter. The average expected and actual blood loss did not differ (Difference=0). No wound hematomas were observed. No post-operative bleeding was documented.

In study GENA-13:

- One major surgery required 36 post-operative infusions (23 EDs): one patient underwent emergency Evacuation Hemarthrosis of the left knee by puncture (Installation of splint) following intensive physical activity. Information on blood loss were not available. No wound hematomas were observed post-operatively. No post-operative bleeding was documented.

Considering the heterogeneity in the surgical procedures and local routine protocols for post-surgical prophylaxis to prevent post-surgical bleeding in different hospitals, the number of post-surgical infusions may vary and do not reflect successful peri-operative prophylaxis in haemophilia patients. The higher number of infusions for some surgeries can be considered to reflect expected variability in routine post-surgical prophylaxis and may not be unusually high. In addition, several of the procedures were orthopaedic procedures that may require additional coverage during physical therapy when regaining mobility.

Assessment of the WSA's response

The MAH clarified that large heterogeneity among routine protocols for surgical prophylaxis was present at different study sites. Moreover, the MAH detailed 5 major surgeries that required >30 post-surgical prophylactic infusions. These procedures included the following: i) emergency appendectomy with post-operative wound infection (75 post-op. infusion, 53 EDs), ii) plate osteosynthesis of distal Tibia (42 post-op. infusions, 21 EDs), iii) total knee replacement with post-surgical bleeding (45 post-op. infusions, 36 EDs), iv) synovectomy upper ankle joint (38 post-op. infusions, 32 EDs), v) evacuation haemarthrosis (36 post-op. infusions, 23 EDs).

Provided details on the major surgeries and underlying reasons for the high number of post-op. infusions are acknowledged. It is further acknowledged that routine practice for surgical prophylaxis can vary markedly in this respect among local study sites.

It should be noted in conclusion that presented data for prophylaxis of major surgeries in the integrated GENA-analysis do not well align with data presented in the Nuwiq EPAR, but rather reflect variability of routine use.

Conclusion

Issue not further pursued.

Question 9

Integrated Safety Analysis

a. Apparently, one patient (GENA-21/ GENA-21B) experienced a total of 5 ADRs (3x dizziness, 1x malaise, 1x chest pain). The MAH is asked to provide additional clarification for this accumulation of ADRs and to comment on any potential predisposing medical history.
b. Tightness of the chest is described SmPC and the package leaflet as possible side effect (Sections 4.4. and 4.8 of Annex I, Section 4 of Annex III). As from the integrated analysis, the ADR of chest pain (possible causality, mild severity, outcome:

recovered/resolved) is not included in the tabulated list of adverse reactions of the current SmPC. Clarification is requested.

c. Study procedures for FVIII inhibitor testing appear to be decoupled from the requirements set out in the FVIII guideline. The MAH is requested to outline how many subjects had been scheduled for inhibitor testing and how many finally have been tested according to the schedule outlined in the FVIII Guideline. Clarifications should be accompanied by an expert statement on data validity.

Summary of the WSA's response

a. The MAH would like to clarify that there was no accumulation of ADRs in a single patient, the two patients noted from GENA-21 and GENA-21b study are two different study subjects:

   - Malaise and dizziness in one patient in study GENA-21 were considered temporally associated with Nuwiq administration, were nonserious, and resolved.
   - Chest pain and dizziness (2 events) in one patient in study GENA-21b were considered temporally associated with Nuwiq administration by the investigator, and occurred 12.3 hrs, 19.5 hrs and 37.3 hrs following an infusion of Nuwiq, respectively. The ADRs were mild, non-serious, and resolved.

b. The MAH has committed to update the SmPC to include the ADRs from GENA-21b study by March 2022.

c. Appendix 3 submitted as part of the response, showed the number of inhibitor tests per patient and per visit schedule according to EMA/CHMP/BPWP/144533/2009 guideline. The total number of inhibitor tests performed per time point are presented in Table 8.

Table 8: Total number of Inhibitor Tests Per Visit Schedule in GENA pool

Time points	Total number of tests per time point / Number of patients tested per time point
Screening	163 / 163
ED 10-15	25 / 25
ED 50-75	83 / 78
ED≥100	603 / 156
Other timepoints between screening and ED 100	209 / 191

Assessment of the WSA's response

For the integrated safety analysis, the MAH clarified that there was no accumulation of ADRs in a single patient. In addition, it was committed to update the SmPC in order to include the ADR of chest pain (GENA-21b study) in March 2022. As stated above for the GENA-99 study (see Question 4) the inhibitor testing procedures underlying the integrated analysis deviate from recommendation made in the EMA FVIII Guideline. There is no consistent testing schedule which foresees that i) a recovery and inhibitor test in a central laboratory should confirm that the patient is inhibitor negative at study entry and ii) inhibitor and recovery testing at ED10-15, ED50-75, and at ED~100 (as recommended in the EMA Guideline). Of the GENA-Pool including N=216 subjects, only a minority of the subjects have been tested consequently for inhibitors, in particular at the recommended time points of ED10-15 (N=25/216; 11%) and ED 50-75 (N=78/216; 36%). However, it was confirmed that a majority of patients (N=191/216; 88%) has been tested at other time points between screening and before accumulating ≥100 EDs. No patient in the GENA-Pool was tested positive for FVIII inhibitors or had clinical symptoms suspicious of inhibitor formation. As there is no overall evidence of an increased immunogenicity risk for Nuwiq, this issue is not further pursued.

Conclusion

Issues resolved or not further pursued.

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly.

Of Note: An Article 46 procedure has not been submitted and evaluated for the GENA-99-Study.