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Human Medicines Division

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

Nuwiq

simoctocog alfa

Procedure no: EMEA/H/C/002813/P46/014

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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1. Introduction

On 25th September 2020, the MAH submitted the final study report of the completed paediatric study GENA-05 for Nuwiq/Vihuma according to Article 46 of Regulation (EC) No 1901/2006. In addition, an updated Critical Expert Overview has been provided that further includes information about the recently completed GENA-40 trial (a Phase 3b study in Chinese PTPs ≥6 years). GENA-05 was a prospective, open-label, non-controlled trial to evaluate the immunogenicity, efficacy and safety of treatment with Human-cl rhFVIII in Previously Untreated Patients (PUPs) with severe haemophilia A. The most recent EMA guidelines no longer require formal PUP studies to be conducted. However, the EMA guidelines available at the time of initiation of this study stipulated a requirement for a paediatric study in PUPs. With implementation of Protocol Amendment 04, the study was to be completed in the 4th quarter of 2018 for all patients, except those continuing ITI treatment. The ITI portion of GENA-05 was clinically completed in March 2020. Interim data of this study were already presented to EMA within procedure EMEA/H/C/002813/II/0017/G (approved: 14 September 2017).

As stated in the Cover Letter, dated 24 September 2020, no amendments to be introduced to the Product Information, and thus no regulatory consequences, have been identified by the MAH.

Scientific discussion

1.1. Information on the development program

Human-cl rhFVIII (simoctocog alfa), currently marketed as Nuwiq and its duplicate Vihuma was approved in Europe in July 2014 for the treatment and prophylaxis of bleeding in patients with haemophilia A in all age groups. The study concerned by this article 46 procedure (GENA-05) has been conducted as part of the clinical development program of *Human-cl rhFVIII*. A line listing of all non-clinical and clinical studies included in this program is annexed to this report.

GENA-05 was conducted to fulfil the required evaluation of at least 100 PUPs for a minimum of 100 EDs as stipulated by the EMA CHMP guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products that had been available at the time of study initiation. As such, the conduct and design of GENA-05 complied with an agreed PIP. However, in light of the latest update of this guideline, which removed the requirement of formal PUP studies, the main study was completed prematurely in December 2018.

1.2. Information on the pharmaceutical formulation used in the study

Human-cl rhFVIII (simoctocog alfa) is a B domain-deleted recombinant human blood coagulation factor VIII (rhFVIII) concentrate for intravenous use. The protein is expressed in a human embryonic kidney (HEK) cell line derivative (HEK293F) adapted to grow in serum-free culture medium. *Human-cl rhFVIII* is supplied as lyophilised powder with nominal potencies of 250 IU, 500 IU, 1000 IU or 2000 IU per vial, to be reconstituted with 2.5 mL of water for injection.

1.3. Clinical aspects

1.3.1. Introduction

The MAH submitted a final report for:

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

1.3.2. Clinical study

Clinical study number and title

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

Description

GENA-05 was a prospective, multicentre, multinational, open-label, non-controlled phase 3 study. The aim of this study was to investigate the immunogenicity, haemostatic efficacy and safety of *Human-cl rhFVIII* in at least 100 previously untreated patients (PUPs) with severe haemophilia A (FVIII:C <1%). Patients who developed FVIII inhibitors were offered to start immune tolerance induction (ITI) with a maximum duration of 36 months. GENA-05 was initiated in 2013 and was clinically completed in December 2018, with the ITI phase finishing in March 2020. Upon study completion, patients could enter into the extension study GENA-15.

Methods

Objective(s)

Primary:

The primary objective of this clinical study was to investigate the immunogenicity of *Human-cl rhFVIII* in 100 evaluable PUPs suffering from severe haemophilia A (FVIII:C <1%).

Secondary:

- To assess the efficacy of *Human-cl rhFVIII* during prophylactic treatment (based on the frequency of spontaneous break-through bleeds)
- To assess the efficacy of *Human-cl rhFVIII* during treatment of bleeds
- To assess the efficacy of *Human-cl rhFVIII* in surgical prophylaxis
- To assess the safety and tolerability of *Human-cl rhFVIII*

Study design

GENA-05 was designed as a prospective, multicentre, multinational, open-label, non-controlled phase 3 study in 100 evaluable male PUPs (i.e. previously untreated patients) suffering from severe haemophilia A (FVIII:C <1%).

For each patient, the exposure to *Human-cl rhFVIII*, the efficacy of *Human-cl rhFVIII* in the prevention and the treatment of bleeds, the frequency of break-through bleeds in case of prophylactic treatment, the efficacy in surgical prophylaxis, and the overall safety and tolerability of *Human-cl rhFVIII* were thoroughly assessed. In the course of the follow-up visits (i.e. every 3-4 exposure days [EDs] until ED

20, then every 10-12 EDs until ED 100), FVIII inhibitor levels (primary endpoint) were assessed for each patient. An inhibitor was assessed to be positive if the modified Bethesda assay (Nijmegen modification) resulted in a titre ≥0.6 BU/mL at any time point during the observation period. Inhibitor activity was determined centrally at the following time points: At baseline (Screening Visit), every 3-4 EDs until ED 20, every 10-12 EDs or every 3 months ±2 weeks (whichever came first) after ED 20, at study completion; at any time in the case of a suspicion of inhibitor development. In case of a positive inhibitor result, an inhibitor re-testing using a second separately drawn sample was to be performed centrally; the result of the second sample was taken as the final result for the time point. Low titre inhibitors were defined as ≥0.6 to <5 BU/mL, high-titre inhibitors were defined as ≥5 BU/mL.

Patients who developed a clinically significant and non-transient FVIII inhibitor were offered to start ITI with the IMP. Inhibitors that `disappeared´ without any clinical signs or symptoms, where no FVIII dosing increase was required, and that turned to <0.6 BU/mL within a period of 6 months after first detection, were regarded as "transient". In case of a positive FVIII inhibitor (non-transient) but no ITI initiation within 1 year, the patient had to be withdrawn from the study.

The efficacy of *Human-cl rhFVIII* in prophylactic treatment was evaluated based on the frequency of spontaneous breakthrough bleeds per months and was calculated and assessed as excellent, good, moderate or poor:

- *Excellent:* Less than 0.75 spontaneous BEs per month
- *Good:* Between 0.75 and 1 spontaneous BEs per month
- *Moderate:* Between more than 1 and 1.5 spontaneous BEs per month
- *Poor:* More than 1.5 spontaneous BEs per month

At the end of a BE, the following efficacy assessment was made by the patient's parent(s)/legal guardian(s) (together with the investigator in case of on-site treatment):

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

The occurrence of AEs and changes in concomitant medication were checked and documented at each follow-up visit. A patient completed the study by reaching 100 EDs, or after a maximum study participation period of 5 years from screening, or (with implementation of Protocol Amendment 04) study completion in the 4th quarter of 2018 for all patients except those continuing ITI treatment. In patients who developed FVIII inhibitors and start ITI treatment, the maximum length of ITI was to be 36 months.

Study population /Sample size

GENA-05 was open to male previously untreated patients (PUPs) with severe haemophilia A (FVIII:C <1%). The patient population mainly entails newborns or infants; however, there was no limitation of age for study admission. 100 evaluable PUPs were to be enrolled in this study. This sample size was chosen to satisfy CHMP recommendations current at the time the study was initiated.

Treatments

Prophylactic treatment was recommended, but finally, it was the decision of the responsible treating physician whether patients were treated prophylactically or on demand. Patients could switch from on-demand to prophylactic treatment, or from prophylactic to on-demand treatment during the course of the study.

Prophylactic treatment:

Patients were to be treated prophylactically with a recommended dose of 20-50 IU FVIII/kg body weight (BW). Starting prophylaxis with the first bleeding episode (BE) was highly recommended. The frequency of treatment depended on the patient's clinical situation. For example, prophylaxis could be initiated with every other day injections (in order to keep the FVIII trough level >1%), or with once weekly injections, followed by twice and three times weekly, and every other day treatment. In cases of inadequate response, *Human-cl rhFVIII* administration frequency or dose adjustments could be considered at the Investigator's discretion.

On-demand treatment:

In case of any bleed, the patients could be treated on-demand. The dosage and duration of treatment of spontaneous or traumatic bleeds depended on the location and the extent of bleeding as well as on the clinical situation of the patient. Dosage recommendations were given as follows:

- Minor haemorrhage: 20-30 IU FVIII/kg BW to achieve an intended target peak level of about 40% to 60%. Repeat dose every 8-24 hours until BE is resolved.
- Moderate to major haemorrhage: 30-40 IU FVIII/kg BW to achieve an intended target peak level of about 60% to 80%. Repeat dose every 6-24 hours until BE is resolved.
- Major to life-threatening haemorrhage: initial dose of 40-60 IU FVIII/kg BW to achieve an intended target peak level of 100% to 120%. Repeat dose of 20-50 IU FVIII/kg BW every 6-12 hours until BE is resolved.

Surgical prophylaxis:

The dosage and duration of treatment with *Human-cl rhFVIII* depended on the type of surgery and the patient's individual incremental FVIII recovery. Dosage recommendations were given as follows:

- Minor surgeries including tooth extractions: 25-30 IU FVIII/kg BW starting within 3 hours prior to surgery to achieve an intended target peak level of >30%. Repeat one dose every 12-24 hours if needed. Trough levels should be maintained at ≥30%.
- Major surgeries: 40-60 IU FVIII/kg BW within 3 hours prior to surgery to achieve an intended target peak level of approximately 100%. Repeat if necessary after 6-12 hours initially and for at least 6 to 14 days until healing is complete and recurrence to regular prophylactic treatment is possible. Trough levels should be maintained at >50%.

FVIII recovery investigation (optional):

Patients received 40 IU FVIII/kg BW for *in-vivo* recovery evaluation. Blood samples were taken at baseline, 15 minutes and 1 hour after the Investigational Medical Product (IMP) administration.

Immune tolerance induction (ITI) (if applicable):

Patients who developed a clinically significant and non-transient inhibitor were offered to start ITI with the IMP. The modified Bonn Protocol for inhibitor elimination was recommended:

- Low responders (<5 Bethesda Units [BU/mL]) should receive 50-100 IU FVIII/kg BW daily or every second day. In case the inhibitor increases to 5 BU/mL or more, the patient should switch to the high responder regimen.

- High responders (≥5 BU/mL) should receive 100-150 IU FVIII/kg BW every 12 hours.

Once the inhibitor had been eliminated (<0.6 BU/mL), the FVIII recovery was ≥66% of normal, and the half-life of FVIII was at least 6 hours, a continuous reduction of about 10% of the initial ITI dosage was to be initiated, until the patient had reached a prophylactic treatment regimen of 30-50 IU FVIII/kg BW every other day. Any other ITI approach was possible.

Outcomes/endpoints

Criteria for evaluation were:

- Immunogenicity: FVIII inhibitor screen
- Prophylactic Treatment: Frequency of spontaneous breakthrough bleeds under three times weekly or every other day prophylactic treatment, and in case of surgical prophylaxis.
- Efficacy: Efficacy assessment at the end of each BE
- FVIII recovery Investigation: In vivo recovery (calculated from the FVIII plasma levels before infusion and the peak level obtained from the 15 minutes and 1 hour post-infusion samples)
- Safety: Adverse events, Vital signs (blood pressure, heart rate, respiratory rate and body temperature, Safety laboratory parameters (red blood cell [RBC] count, white blood cell [WBC] count, haemoglobin, haematocrit, platelet count, alanine amino transferase [ALT], aspartate transaminase [AST], serum creatinine)

Statistical Methods

The statistical analyses of the primary and secondary endpoints are descriptive. No inferential analysis involving formal testing was planned in this non-controlled trial.

Results

Recruitment/ Number analysed

Of the 110 enrolled patients, 108 had data collected post-treatment with *Human cl rhFVIII* and were included in the ITT and safety analysis (SAF) populations. The patients were enrolled and treated at 38 investigational centres in Belarus, Canada, France, Georgia, Germany, India, Italy, Moldova, Morocco, Poland, Portugal, Russian Federation, Slovenia, Spain, Ukraine, United Kingdom, and United States. 103 of the enrolled patients had at least one prophylactic treatment (i.e. at least one administration of *Human-cl rhFVIII* with prophylaxis documented as the reason for treatment) and constitute the PROPH population; 50 patients were in the population of subjects on continuous prophylaxis (PROPHcont). Eighteen of the 28 patients who developed FVIII inhibitors started ITI treatment. In the 108 treated patients, 1199 BEs were documented in 99 patients. Of these, 931 BEs in 94 patients were documented as treated with *Human-cl rhFVIII* and therefore constituted the BLEED population. A total of 52 surgeries were documented in 37 patients. Twenty-six of these surgeries (in 24 patients) were performed under *Human-cl rhFVIII* treatment and were therefore included in the SURG population.

Baseline data

Age at screening in the safety population ranged from 0 to 146 months, with a median of 9.5 months. The majority of patients were White (82.4%); 13.0% were Asian and 1 patient (0.9%) was American Indian or Alaska Native. Overall, 42 (38.9%) had a family history of haemophilia, 13 (12.0%) had a

family history of inhibitors to FVIII, and 73.1% of patients had a gene defect associated with a high risk of inhibitor formation.

Immunogenicity results

The primary endpoint of this study was the evaluation of FVIII-inhibitor development in PUPs treated with *Human-cl rhFVIII*. An inhibitor was assessed to be positive if the modified Bethesda assay (Nijmegen modification) resulted in a titre ≥0.6 BU/mL at any time point during the observation period. Of the 105 patients in the ITT population with at least one inhibitor test after ED1, 28 (26.7%; 95% CI: 18.5-36.2) developed inhibitors, all with ≤34 EDs prior to detection; 17 (16.2%; 95% CI: 9.7-24.7) patients developed high titre inhibitors and 11 (10.5%; 95% CI: 5.3-18.0) patients developed low titre inhibitors.

Table 1: Statistics on incidence of FVIII inhibitor development

Incidence of inhibitors[1]	ITT Population N=108	PP Population N=95
n (patients with at least one inhibitor test after ED1)	105	95
High titre inhibitor (≥5 BU/mL)	17 (16.2%) 95% CI: 9.7-24.7	15 (15.8%) 95% CI: 9.1-24.7
Low titre inhibitor (<5 BU/mL)	11 (10.5%) 95% CI: 5.3-18.0	11 (11.6%) 95% CI: 5.9-19.8
Any inhibitor (≥0.6 BU/mL)	28 (26.7%) 95% CI: 18.5-36.2	26 (27.4%) 95% CI: 18.7-37.5

[1] Inhibitor occurrence: any inhibitor occurrence (titres ≥0.6 Bethesda units (BU/mL)) confirmed by retest of same sample and test of different sample at subsequent time point, or confirmed by test and retest of different sample at subsequent time point, or confirmed by test of 2 subsequent samples at different time points (if retests not available), or confirmed as high titre inhibitor (titres ≥5 BU/mL) by test and either retest or one test or retest at least one subsequent time point.

95% CI=lower and upper bound of a 95% exact confidence interval for the inhibitor rate; BU=Bethesda units; ITT=intent to treat population; n=number of patients with at least one inhibitor test after ED1; PP=per protocol population.

Source: Table 11, CSR

Of the 28 patients who developed an inhibitor, 25 did so with ≤20 EDs prior to detection. Results were comparable in the PP population. The median number of EDs to first confirmed inhibitor activity was 11.0 days (range: 4-34). Logistic regression and Cox regression analyses indicated that high risk F8 gene mutation and age ≤12 months at first treatment are independent prognostic factors for the development of inhibitors. No PUPs with non-null *F8* mutations developed inhibitors.

Efficacy results

In GENA-05, data from inhibitor-free periods were the focus of the efficacy analyses to avoid bias that may result from the neutralising effect of inhibitors and/or the haemostatic effect of the increased doses administered during ITI treatment.

Prophylactic treatment:

For the 103 subjects receiving prophylactic treatment in GENA-05, the mean (range) prophylactic dose per injection was 37.4 (16.1-96.0) IU/kg and the mean (range) prophylactic dose per month was 288.4 (59-1455) IU/kg.

Efficacy of prophylactic treatment was evaluated by the monthly rate of spontaneous break-through bleeds (MBR) during time of prophylactic treatment assessed as excellent, good, moderate or poor (secondary endpoint). The overall prophylaxis efficacy assessment for spontaneous BEs at end of study (a programmed, objective assessment) was excellent (MBR <0.75) in 100 (98.0%) patients, moderate

(MBR >1–1.5) in 1 (1.0%) patient, and poor (MBR >1.5) in 1 (1.0%) patient. For all types of BEs, the mean MBR was 0.385 (95% CI: 0.299–0.472) and the mean annualised bleeding rate (ABR) was 4.693 (95% CI: 3.635–5.751). For spontaneous BEs, the mean MBR was 0.080 (95% CI: 0.035–0.125) and mean annualised bleeding rate (ABR) was 0.976 (95% CI: 0.431–1.521). For patients on continuous prophylaxis (defined as a prophylactic treatment period of at least 169 calendar days, N=50), bleeding rates were lower: For spontaneous BEs, the mean MBR was 0.044 (95% CI: 0.019–0.069) and the mean ABR was 0.536 (95% CI: 0.233–0.839) and for all types of BEs, the mean MBR was 0.296 (95% CI: 0.207–0.386) and the mean ABR was 3.609 (95% CI: 2.523–4.694).

Table 2: Summary of annualised bleeding rates (ABR) reported during inhibitor-free periods in GENA-05

	PROPH population (N=103)		PROPHcont population (N=50)	
	ABR [a]		ABR [a]	
Parameter	**n**	**Mean (95%CI)**	**n**	**Mean (95%CI)**
Spontaneous BEs	102	0.976 (0.431–1.521)	50	0.536 (0.233–0.839)
Spon. BEs joint bleeding	102	0.331 (0.165–0.497)	50	0.339 (0.093–0.584)
Spon. BEs no joint bleeding	102	0.645 (0.129–1.160)	50	0.197 (0.061–0.334)
Traumatic BEs	102	3.317 (2.475–4.159)	50	2.802 (1.789–3.816)
Traum. BEs joint bleeding	102	0.920 (0.509–1.332)	50	0.543 (0.324–0.762)
Traum. BEs no joint bleeding	102	2.397 (1.654–3.139)	50	2.259 (1.254–3.264)
All types of BEs	102	4.693 (3.635–5.751)	50	3.609 (2.523–4.694)
All types of BEs joint bleeding	102	1.342 (0.851–1.834)	50	1.039 (0.497–1.580)
All types of BEs no joint bleeding	102	3.350 (2.378–4.323)	50	2.570 (1.562–3.578)

[a] Annualized rate of BEs during inhibitor-free periods (Number of BEs under prophylaxis during inhibitor-free periods/days under prophylactic treatment during inhibitor-free periods) x 365.25 days.
CI=confidence interval; ABR=Annualised Bleeding Rate; n=number of patients; PROPH=study population of patients receiving prophylaxis; PROPHcont= study population of patients on continuous prophylaxis; Spon.=spontaneous; Traum.=traumatic.

Source: Table 28, CSR

Treatment of bleeding episodes:

Of the 108 patients in the study, 99 patients experienced BEs, 94 patients had BEs that were treated with *Human-cl rhFVIII*, and 85 patients had BEs during inhibitor-free periods that were treated with *Human-cl rhFVIII*. The number of BEs in the BLEED population during inhibitor-free periods was 808 (in 85 patients); 294 (36.4%) occurred in 66 patients during prophylactic treatment, 502 (62.1%) in 51 patients during on-demand treatment, 4 (0.5%) in 3 patients during surgical prophylaxis, and 8 (1.0%) in 4 patients during ITI treatment (patients could experience BEs in more than one of these

categories). Of these 808 BEs, 196 (24.3%) were documented as spontaneous, 584 (72.3%) as traumatic, 4 (0.5%) post-operative, and 24 (3.0%) as other or unknown. Specific-site bleeds were most common in the knee (93 [11.5%]), oral cavity and ankle (both 76 [9.4%]), and arm, leg andnose (each 72 [8.9%]). 'Other' sites of bleeding accounted for the overall majority of bleeds characterised by multiple sites: 294 (36.4%). The majority of BEs during inhibitor-free periods (524 [64.9%]) were minor; 274 (33.9%) were moderate to major, 7 (1.9%) were major to life-threatening, and 3 (0.4%) were of unknown severity. The efficacy assessment at the end of a BE was based on an objective four-point scale and done by the patient's parent(s)/legal guardian(s) (together with the Investigator in case of on-site treatment). The majority of BEs were rated as having excellent (63.4%, 510 BEs) or good (29.5%, 237 BEs) treatment efficacy; treatment efficacy was rated as moderate for 51 (6.3%) BEs and as none for 6 (0.7%) BEs.

Table 3: Efficacy of *Human-cl rhFVIII* the treatment of bleeding episodes

		Number (%) of BEs
Bleed category	**Rating**	**BLEED population During Inhibitor-Free Periods n=804 missing=4**
Any bleed	Excellent	510 (63.4)
	Good	237 (29.5)
	Moderate	51 (6.3)
	None	6 (0.7)
Severity:	Excellent	376 (71.9)
Minor	Good	130 (24.9)
	Moderate	13 (2.5)
	None	4 (0.8)
Severity:	Excellent	133 (48.5)
Moderate to	Good	104 (38.0)
Major	Moderate	35 (12.8)
	None	2 (0.7)
Severity:	Excellent	1 (14.3%)
Major to	Good	3 (42.9)
Life-threatening	Moderate	3 (42.9)
	None	0

n=number of BEs

Source: Table 31, CSR

The majority of BEs during inhibitor-free periods (91.9%) were treated with 1 or 2 infusions. The mean number of infusions per episode was 1.4 infusions (± 1.08, range: 1-11), and the mean dose per BE/kg body weight was 51.3 IU/kg (± 49.54, range: 15-663).

Surgical prophylaxis:

A total of 24 patients had 26 surgeries that were included in the SURG population. Of these, 13 patients had minor surgeries and 11 patients had major surgeries. Twenty-one of these surgeries had an overall efficacy assessment (based on objective 4-point scales) performed jointly by the haematologist and surgeon (the assessment was not performed for 5 surgeries), with 15 rated as having excellent efficacy, 3 having good efficacy, 2 moderate efficacy, and 1 with efficacy rated as "none". The surgery with efficacy rated as "none" was performed in a patient with inhibitors. Patients received *Human-cl rhFVIII* prior to surgery (loading doses) and – if indicated – during surgery (maintenance doses), plus potentially after surgery up to discharge from the hospital. Infusions from prior to surgery until discharge are summarised in Table 4 below.

Table 4: Statistics on *Human-cl rhFVIII* Dosing for Surgical Coverage

Type of surgery	Minor (n=15)		Major (n=11)		All (n=26)	
	Mean (± SD)	Range	Mean (± SD)	Range	Mean (± SD)	Range
Total dose (IU)	5390.0 (±6079.3)	500-23500	12022.7 (±4841.8)	4000-19250	8196.2 (±6422.0)	500-23500
Total dose (IU/kg)	440.7 (±470.5)	20.8-1807.7	1030.8 (±412.2)	271.3-1490.7	690.4 (±529.5)	20.8-1807.7
Total dose per infusion (IU/kg)	45.0 (±22.4)	20.8-90.9	59.2 (±23.4)	38.8-112.4	51.0 (±23.5)	20.8-112.4
Pre-operative loading dose (IU/kg)	49.8 (±36.7)	0-125.0	56.3 (±39.1)	0-100.0	52.6 (±37.1)	0-125.0
Maintenance dose (IU/kg)	NA	NA	NA	NA	9.5 (±27.9)	0-112.4
Dose after end of surgery (IU/kg)	NA	NA	NA	NA	624.8 (±521.5)	0-1769.2

N=number of patients; n=number of surgical procedures; NA=not available

Source: Table 37, CSR

FVIII Recovery Determinations

Recovery determinations were optional (but recommended) within the study. Notable FVIII plasma levels were evident in the blood at 15 minutes post-administration, and levels remained at a considerable concentration at 1 hour. For the ITT population in patients without inhibitors the mean incremental IVR (% per IU/kg) ranged from 1.43 to 1.78.

Immune tolerance induction

Efficacy of *Human-cl rhFVIII* as ITI was examined in 18 patients who developed FVIII inhibitors and continued into the ITI phase. The mean age at screening was 7.4 months (range 0–17). Complete success of a patient's ITI was defined as: 1) FVIII inhibitor negative (<0.6 Bethesda units [BU]/mL) at two sequential measurements; 2) FVIII recovery ≥0.99%/(IU/kg) (= 66% of 1.5 %(IU/kg); 3) FVIII terminal half-life ≥6 hours.

Of the 18 patients included in the ITI sub-study, 4 (22.2%) patients finished ITI with complete success according to the investigator. Additionally, 1 patient had ITI treatment that was assessed as not successful by the investigator despite meeting all 3 success criteria. Another patient was documented as having met all 3 success criteria before withdrawing consent and discontinuing the study and was not

assessed as a complete success by the investigator. Therefore, the proportion of patients who had complete success of ITI according to investigator assessment or criteria from study data was 6/18 (33.3%). One patient had partial success (2 criteria met) and 1 patient had a partial response (1 criterion met) [5.6% each]. The remaining 10 patients had ITI failure, fulfilling none of the success criteria (3 due to therapy failure, 5 due to reaching 36 months of ITI treatment without reaching any success criterion, 1 due to withdrawn consent, and 1 due to permanent switch to another FVIII product).

Table 5: Summary of Patient Outcome in the ITI Sub-Study

Patient ID	Age at first ED (months)	Peak inhibitor titre (BU/mL)	*F8* gene mutation type/class/ risk	EDs in ITI sub-study	ITI completed according to protocol	Complete success of ITI according to investigator	Success of ITI according to criteria from study data/ Number of criteria fulfilled	Reason for completion/ discontinuation
		12.9 (HT)	Large deletion/ Null/ High	79	No	No	Failure/0	Consent withdrawn
		16.6 (HT)	Intron 1/ Null/ High	1083	Yes	Yes	Complete success/2	Complete success of ITI (full PK assessment was not feasible in this small patient so the half-life criterion could not be assessed, but good FVIII trough levels were achieved, and the other criteria were met)
		1396.5 (HT)	Intron 22/ Null/ High	1096	Yes	No	Failure/0	Maximum ITI period of 36 months
		6.2 (LT)	Large deletion/ Null/ High	715	Yes	Yes	Complete success/3	Complete success of ITI
		203.4 (HT)	Nonsense mutation/ Null/ High	1061	Yes	No	Failure/0	Maximum ITI period of 36 months
		744.7 (HT)	Large deletion/ Null/ High	200	No	No	Failure/0	Therapy failure
		531.4 (HT)	Intron 22/ Null/ High	456	No	No	Failure/0	Therapy failure
		38.2 (HT)	Nonsense mutation/ Null/ High	1163	Yes	No	Partial success/2	Maximum ITI period of 36 months
		2.3 (LT)	Intron 22/ Null/ High	523	Yes	Yes	Complete success /3	Complete success of ITI
		265.6 (HT)	Small deletion/ Null /High	1088	Yes	No	Failure/0	Maximum ITI period of 36 months
		4.0 (LT)	Intron 22/ Null/ High	955	Yes	No	Failure/0	Maximum ITI period of 36 months (inhibitors reoccurred after fulfilment of success criteria)
		822.4 (HT)	Intron 22/ Null/ High	535	No	No	Failure/0	Permanent switch to other FVIII product

cont.

3.0 (LT)	Intron 22/ Null/ High	498	Yes	No	Complete success/3	Maximum ITI period of 36 months
300.5 (HT)	Small deletion/ Null /High	198	No	No	Failure/0	Therapy failure
3.1 (LT)	Intron 22/ Null/ High	667	No	No	Complete success/3	Consent withdrawn
2.5 (LT)	No mutation detected	271	Yes	Yes	Complete success/3	Complete success of ITI
137.6 (HT)	Intron 22/ Null/ High	1095	Yes	No	Failure/0	Maximum ITI period of 36 months
47.7 (HT)	Intron 22/ Null/ High	1104	Yes	No	Partial response /1	Maximum ITI period of 36 months

BU=Bethesda unit; EDs=exposure day; HT=high titre; ITI=immune tolerance induction; LT=low titre;
Source: Listings 16.2.1.2.2, 16.2.8.3 and 16.2.8.4

Source: Table 4, CSR Addendum

Other Safety results

The safety population comprised all 108 patients who received a total of 25,551 infusions of *Human-cl rhFVIII* across all assessments in the main study. Including the final phase of ITI treatment, patients had a mean (range) of 196.7 (1-1175) days of exposure to *Human-cl rhFVIII*, a mean of 258.6 (1-2348) infusions, and a mean total dose of 21,339 (28-227,551) IU/kg. Under prophylaxis, patients had a mean of 70 EDs (median: 89 EDs, range: 1-115) and received a mean total dose of 2,659 IU/kg (median: 2,805 IU/kg, range: 28-9,313).

Overall, 101 (93.5%) patients experienced treatment-emergent AEs. During the main study these were observed after 652 out of 25,551 infusions (2.6%) administered in the SAF population. Of the 108 patients in the SAF population, 95 (88.0%) experienced mild AEs, 54 (50.0%) moderate AEs, and 27 (25.0%) severe AEs. The most commonly reported AEs were pyrexia (56.5% patients), naso-pharyngitis (32.4%), Factor VIII inhibition (25.9%), anaemia (19.4%), and rhinitis (18.5%). Eighty-eight SAEs were documented in 48 (44.4%) patients. Two patients had AEs that led to the permanent discontinuation of study drug. These were a case of urticaria and an event of Factor VIII inhibition [primary reason for discontinuation was not initiating ITI treatment]). There were no deaths in this study.

Seventy-eight patients (72.2%) experienced AEs that were temporally associated with 341 infusions, i.e. they occurred within 24 hours of the respective infusion. Based on the sponsor's assessment, a total of 71 related AEs were recorded in 45 PUPs. In addition to FVIII inhibition (31 AEs in 28 patients), these included 28 cases of pyrexia in 20 (18.5%) patients, 5 cases of rash in 5 (4.6%) patients, 4 cases of hypersensitivity in 2 (1.9%) patients, 2 cases of urticaria in 1 (0.9%) patient, and 1 case of chills in 1 (0.9%) patient. At least possibly related SAEs (according to the investigator's assessment) were reported in 29 patients. These SAEs were Factor VIII inhibition (28 patients) and rash (1 patient). The only related AE reported in the final phase of ITI treatment was a case of FVIII inhibitor relapse.

1.3.3. Discussion on clinical aspects

As part of this Article 46 procedure the MAH submitted the final study report of GENA-05 together with an updated Critical Expert Overview. The aim of this phase 3 study was to investigate the immunogenicity, haemostatic efficacy and safety of *Human-cl rhFVIII* in previously untreated patients (PUPs) with severe haemophilia A (FVIII:C <1%). In this study, data was collected from 108 previously untreated children at 38 different investigational centers.

GENA-05 was primarily conducted to fulfil the required evaluation of at least 100 PUPs for a minimum of 100 EDs as stipulated by the EMA CHMP guideline on the clinical investigation of recombinant and

human plasma-derived factor VIII products (EMA/CHMP/BPWP/144533/2009 rev. 1) that had been available at the time of study initiation. As such, the conduct and design of GENA-05 complied with an agreed PIP. However, in light of the recent update of this guideline which removed the requirement of formal PUP studies, GENA-05 was completed prematurely (in the 4th quarter of 2018), except for patients on ITI treatment.

Interim data of GENA-05 were already presented to EMA in 2017 (EMEA/H/C/002813/II/0017/G) which led to removal of the statement "the safety and efficacy of *Human-cl rhFVIII* in previously untreated patients have not yet been established" in section 4.2 and inclusion of the risk of FVIII inhibitor development in PUPs with a frequency category of "very common" in the ADR table of section 4.8 of the Nuwiq/Vihuma SmPC.

The study population of GENA-05 is considered representative of the global population of PUPs with haemophilia A. As expected for PUPs, subjects were very young with a median age of 9.5 months [range: 0 to 146; 58 subjects (~62%) <1 year at enrollment]. Treatment recommendations for initiation of prophylaxis and for the treatment of bleeds were largely comparable to previous trials in paediatric PTPs and generally in line with the posology of *Human-cl rhFVIII* as reflected in the current SmPC. The primary endpoint of GENA-05 was the incidence of inhibitor development. The evaluation of clinical efficacy of *Human-cl rhFVIII* during routine and surgical prophylaxis and the treatment of bleeds constituted secondary endpoints.

Inhibitor development

Of the 105 patients in the ITT population with at least one inhibitor test after ED1, 28 (26.7%; 95% CI: 18.5-36.2) developed inhibitors, all with ≤34 EDs prior to detection. Seventeen (16.2%; 95% CI: 9.7-24.7) patients developed high titre inhibitors, all with ≤24 EDs prior to detection, and eleven (10.5%; 95% CI: 5.3-18.0) patients developed low titre inhibitors, all with ≤34 EDs prior to detection. The reported frequency of inhibitor development of 26.7% in the final report of GENA-05 is largely comparable to the frequency reported in the interim analysis (i.e. 18 of 85 subjects, 21.2%) and does not change the frequency category of "very common" as specified in section 4.8 of the current SmPC. Overall, it is concluded that final data of Study GENA-05 reveal a rate of inhibitor development in the range of what has been reported for different FVIII products, particularly for the class of recombinant FVIII medicines. The SIPPET study is the only prospective, randomised, controlled study to compare the immunogenicity of pdFVIII. In patients treated with rFVIII, the cumulative incidence of all and high-titre inhibitors was 44.5% (95% CI: 34.7–54.3%) and 28.4% (95% CI: 19.6–37.2%), respectively. The cumulative incidence of all and high-titre inhibitors in GENA-05 was 27.9 and 17.6%, respectively. These rates are considerably lower than the rates reported for the rFVIII arm in the SIPPET study, all derived from hamster cell lines (cumulative incidence 44.5% for all inhibitors and 28.4% for high-titre inhibitors), and in line with results obtained for the pdFVIII arm of the SIPPET study (26.8 and 18.6% for all and high-titre inhibitors, respectively). Reference: https://www.thieme-connect.com/products/ejournals/pdf/10.1055/s-0040-1722623.pdf

However, as noted in the Article 31 referral for factor VIII medicines (EMA/765710/2017), comparability of study results is generally hampered by the diversity of study methods and different patient populations evaluated. Notably, the reported rate of inhibitor development has to be interpreted in the context of 23 of the 108 patients included in GENA-05 who received *Human-cl rhFVIII* for only 20 or fewer exposure days, 11 of whom with only 10 or fewer EDs (Listing 16.2.5.3.1). However, upon request the MAH substantiated the reported incidence of inhibitor development by excluding the subsets of inhibitor negative subjects with less than 10, 20, or 50 EDs from the calculation.

Other Safety data

Other safety data obtained in GENA-05 are considered i) comparable to other products of this class, ii) consistent with previous experiences and iii) do not indicate safety issues specific to the group of PUPs.

During GENA-05, a total of 71 related AEs were recorded in 45 PUPs. With the exception of FVIII inhibition (31 AEs in 28 patients), there were 28 cases of pyrexia in 20 (18.5%) patients, 5 cases of rash in 5 (4.6%) patients, 4 cases of hypersensitivity in 2 (1.9%) patients, 2 cases of urticaria in 1 (0.9%) patient, and 1 event of chills in 1 (0.9%) patient. Notably, as a result of the type 2 variation procedure

EMEA/H/C/002813/II/0017/G, ADRs from an allergic context (namely rashes, and urticaria) were collectively referred to by the PT 'Hypersensitivity' that his currently included with a frequency category of 'common' (i.e. ≥1/100 to <1/10) in section 4.8 of the product's SmPC. Upon request, the MAH confirmed that final data of GENA-05 do not change this frequency category.

The comparably high frequency of potentially drug-related pyrexia (i.e. 28 cases in 20 subjects plus an additional event of chills) has to be interpreted in the context of the very young age of the majority of study participants (median age: 9.5 months) and the generally high likelihood of developing pyrexia at this age. The current SmPC lists 'Pyrexia' as a common ADR and results of GENA-05 do not change this frequency category.

In conclusion, results of GENA-05 are considered consistent with the known safety profile of *Human-cl rhFVIII* and do not evoke any new or specific concerns with regard to the treatment of PUPs. The newly reported ADRs are not considered remarkable and have already been reported for *Human-cl rhFVIII* or other products of this class.

Incremental recovery of Human-cl rhFVIII

In GENA-05, recovery determinations were optional (but recommended) in all patients. During the main study, IVR was calculated for a total of 45 inhibitor-free patients and 104 different time points (Listing 16.2.5.12). Based on the chromogenic assay, mean (SD) values calculated for different determination time points (at intervals of 6 months after ED1 and at the completion visit) ranged from 1.43 (± 0.7) to 1.78 (± 0.3) % per IU/kg. Hence, on average values obtained in PUPs were slightly lower than the ones reported in 2 to 5 year old children in GENA-03 [i.e. 1.9 (± 0.3) %/IU/kg, see also SmPC section 5.2]. However, the trend towards lower IVR is considered consistent with the younger age of patients treated in GENA-05 (median age: 9.5 month) and considered sufficiently covered by the statement that especially in younger patients shorter dosage intervals or higher doses may be necessary in section 4.2 of the SmPC.

Haemostatic efficacy in prophylaxis and in the treatment of BEs

In GENA-05, mean doses of *Human-cl rhFVIII* administered per prophylactic infusion (i.e. 37.4 IU/kg) or for the treatment of BEs (i.e. 51.3 IU/kg) were largely comparable to the average doses used in previous trials in paediatric PTPs. For instance, a mean monthly prophylaxis dose of 288.4 IU/kg (range: 59–1455 IU/kg) in GENA-05 compares to a consumption of 330 IU/kg (range: 69–1554 IU/kg) reported in the long-term extension study GENA-15. The median number of infusions administered for the treatment of bleeding episodes was 1 in all paediatric studies with broadly comparable proportions of successfully treated events (i.e. 82.4% in GENA-03, 83.0% in GENA-13, 82% in GENA-40, 92.9% in GENA-05, and 77.5% in GENA-15). Except for a circumcision performed in a patient with high titre inhibitors (efficacy rated 'none'), a CVAD insertion in a patient with low-titre inhibitors and a circumcision performed in a 69 months old boy (both rated 'moderate'), all of the 21 procedures covered by *Human-cl rhFVIII* in GENA-05 (12 major and 9 minor surgeries) had an efficacy rating of 'excellent' or 'good'.

Under prophylaxis, the mean ABR during inhibitor-free periods for all types of bleeds was 4.693 (± 5.39). According to Table 14.2.19.6.1.1, ABRs ranged from 0 to 26.09 with a median of 2.77. Notably, these numbers have to be interpreted in the context of i) a considerable proportion of patients who received prophylaxis for less than 6 months and ii) a highly vulnerable population under study, prone to trauma-induced bleeding. Consistently, a separate analysis restricted to the subgroup of patients on continuous prophylaxis (i.e. ≥169 days, N=50) indicates lower bleeding tendencies with a median ABR of 3 and a range of 0 to 15 (Table 14.2.19.6.1.2). Furthermore, considering only spontaneous BEs, patients on continuous prophylaxis had a median ABR of 0 (range: 0 to 4.58) (Table 14.2.19.4.1.2). Hence, results of GENA-05 essentially confirm haemostatic efficacy of *Human-cl rhFVIII* in prophylaxis and the treatment of BEs in previously untreated patients.

Immune tolerance induction

In GENA-05, efficacy of *Human-cl rhFVIII* in ITI was examined in 18 patients who developed FVIII inhibitors (6 patients with low-titre and 12 patients with high titre inhibitors). Definitions of ITI success

(complete success, partial success and partial response) followed the publication of Kreuz et al. 2016 and success criteria were in line with the International Immune Tolerance Study published in 2012 by Hay and DiMichele. In GENA-05, the proportion of patients with complete success of ITI according to the investigator's assessment or criteria from study data was 6/18 (33.3%). 10 patients (55.6%) had ITI failure, fulfilling none of the success criteria after the 36-month observation period. The number of patients who underwent ITI within the GENA-05 study is too low to draw firm conclusions or to allow comparison with other studies, in different patient populations with dif-ferent ITI regimens. This success rate appears considerably lower than the success rates reported in literature, varying from approximately 45% to 80% depending on the protocol (as e.g. noted in Ryu et al., 2015; doi: 10.5045/br.2015.50.4.248). Furthermore, the reported success rate of ITI has to be interpreted in the context of 5 of the 6 successfully treated patients who had "only" low-titers of FVIII inhibitors, previously shown to often develop a natural (spontaneous) sustained negative inhibitor status (see e.g. Yoo et al. 2016, doi: 10.5045/br.2016.51.1.37 or Caram et al. 2011, doi: 10.1160/TH10-04-0231)On the other hand - and in line with the EMA reflection paper on ITI in haemophilia A (EMA/CHMP/BPWP/153137/2011) - it is agreed with the MAH that comparisons across studies may be confounded by numerous factors, including the use of differing success criteria and analysis methods, differing treatment durations and intensities, and differing patient populations regarding risk factors for ITI failure. However, given the comparably poor ITI outcome reported in GENA-05, it is concluded that a convincing proof of efficacy of *Human-cl rhFVIII* in ITI has yet to be provided.

2. CHMP's overall conclusion and recommendation

In summary, data obtained in previously untreated patients (PUPs) in GENA-05 do not change the favourable benefit risk profile of *Human-cl rhFVIII* in pediatric patients. The presented data do not warrant any substantial update of the Product information and no regulatory actions are expected to be required. Minor changes to the SmPC, namely an update of the numbers of evaluated subjects in section 4.8 and removal of the sentence *"A prospective open-label clinical study in PUPs with severe haemophilia A (<1% FVIII:C) is ongoing"* in section 5.1 should be implemented timely with the next revision of the SmPC. However, prior to a final recommendation, additional clarification on some of the reported clinical outcomes should be provided by the MAH.

☒ **Not fulfilled, additional clarification requested.**

3. Additional clarification requested

1. The reported rate of inhibitor development (i.e. 26%) has been calculated including 23 patients who received *Human-cl rhFVIII* for only 20 or fewer EDs, 11 of whom with only 10 or fewer EDs (as noted in Listing 16.2.5.3.1). Hence, to account for a potential impact of insufficient exposure, the MAH should specify (i.e. re-calculate) the rates of inhibitor development restricting the analysis to subjects with at least 10, 20, or 50 EDs to *Human-cl FVIII*.
2. The presented evaluation of haemostatic efficacy in the treatment of BEs was restricted to inhibitor-free periods. Nevertheless, efficacy was rated 'none' in 6 of the BEs treated with *Human-cl rhFVIII*. For these BEs, the MAH should critically discuss the apparent lack of efficacy.
3. As a result of the type 2 variation EMEA/H/C/002813/II/0017/G, the PT hypersensitivity in the ADR table of the SmPC (section 4.8) covers multiple AEs of allergic symptoms including events of rash and urticaria. Given the at least 12 additional drug-related "allergic" AEs (5 cases of rash, 4 cases of hypersensitivity, 2 cases of urticaria) reported in GENA-05, the MAH should confirm that the frequency category "common" (≥1/100 to <1/10) as specified in the current SmPC for the PT hypersensitivity remains unchanged.
4. Given the 28 additional cases of drug-related pyrexia (plus an additional event of chills) reported in GENA-05, the MAH is requested to confirm that the frequency category "common" (≥1/100 to <1/10) as specified in the current SmPC for the PT pyrexia remains unchanged.
5. The exposure and safety information as summarized in the Critical Expert Overview (Tables 4 and 5) neglect data obtained during the final phase of ITI treatment. The ITI addendum to the CSR solely covers data obtained in the ITI sub-study of GENA-05. Hence, it is not clear which of the AEs reported in the final phase of ITI add to the safety data presented in the main CSR (and the Clinical Expert Overview). Thus, the MAH should provide a comprehensive presentation of safety data obtained in GENA-05 (including the ITI sub-study) and, if necessary, update information on potentially drug-related AEs.

Additional comment for the MAH:

Minor changes to the SmPC, namely an update of the numbers of evaluated subjects in section 4.8 and removal of the sentence *"A prospective open-label clinical study in PUPs with severe haemophilia A (<1% FVIII:C) is ongoing"* in section 5.1 should be implemented timely with the next revision of the SmPC.

4. Assessment of the responses to requested clarifications

Question 1

The reported rate of inhibitor development (i.e. 26%) has been calculated including 23 patients who received *Human-cl rhFVIII* for only 20 or fewer EDs, 11 of whom with only 10 or fewer EDs (as noted in Listing 16.2.5.3.1). Hence, to account for a potential impact of insufficient exposure, the MAH should specify (i.e. re-calculate) the rates of inhibitor development restricting the analysis to subjects with at least 10, 20, or 50 EDs to *Human-cl FVIII*.

MAH's responses

The requested information is provided in the table below. Only a slight increase in the incidence of inhibitors was observed in the ED10, ED20, and ED50 subgroups as compared to total in the ITT population.

Statistics on incidence of inhibitors overall and for the ED10, ED20 and ED50 subgroups

Incidence of inhibitors[1]	ITT Population N=108	PP Population N=95
Total	n=105 28 (26.7%) 95% CI: 18.5-36.2	n=95 26 (27.4%) 95% CI: 18.7-37.5
ED10	n=101 28 (27.7%) 95% CI: 19.3-37.5	n=93 26 (28.0%) 95% CI: 19.1-38.2
ED20	n=99 28 (28.3%) 95% CI: 19.7-38.2	n=93 26 (28.0%) 95% CI: 19.1-38.2
ED50	n=98 28 (28.6%) 95% CI: 19.9-38.6	n=93 26 (28.0%) 95% CI: 19.1-38.2

[1] Inhibitor occurrence: any inhibitor occurrence (titres ≥0.6 Bethesda units (BU/mL)) confirmed by retest of same sample and test of different sample at subsequent time point, or confirmed by test and retest of different sample at subsequent time point, or confirmed by test of 2 subsequent samples at different time points (if retests not available), or confirmed as high titre inhibitor (titres ≥5 BU/mL) by test and either retest or one test or retest at least one subsequent time point.

95% CI=lower and upper bound of a 95% exact confidence interval for the inhibitor rate; ED=exposure days; ED10=at least 10 EDs; ED20=at least 20 EDs; ED30=at least 50 EDs; ITT=intent to treat population; n=number of patients with at least one inhibitor test after ED1; PP=per protocol population.

Assessment of the MAH's responses

The aim of this request was to assess the impact of subjects with little exposure to *Human-cl rhFVIII* on the reported rate of inhibitor development. For this, the applicant was expected to calculate the incidences of inhibitors considering only the subsets of patients with at least 10, 20, or 50 EDs. However, in contrast to the EDs shown in listing 16.2.8.2 3 (i.e. excluding ITI treatment), the applicant apparently did not discriminate between EDs during prophylaxis or ITI. Consequently, since i) three of the subjects with <10 EDs received only one dose of *Human-cl rhFVIII* and were not tested for inhibitors and ii) many of the subjects with <20 EDs during prophylaxis were tested positive and received additional (often extensive) dosing of *Human-cl rhFVIII* during subsequent ITI (Listing 16.2.8.2), only a small number of patients (N=4 with <10 EDs, N=6 with <20 EDs and N=7 with <50 EDs) were excluded from the original analysis. However, considering that the applicant's approach selectively excludes subjects who did not develop an inhibitor, the presented calculations are regarded to result in rather conservative estimates. Since even on the basis of these calculation only a slight increase in the rate of inhibitor development was observed in the ED10, ED20, and ED50 subgroups, there are no outstanding concerns with regard to a relevant impact of subjects with "insufficient" EDs on the reported rate of inhibitor development.

Issue ***resolved.***

Question 2

The presented evaluation of haemostatic efficacy in the treatment of BEs was restricted to inhibitor-free periods. Nevertheless, efficacy was rated 'none' in 6 of the BEs treated with *Human-cl rhFVIII*. For these BEs, the MAH should critically discuss the apparent lack of efficacy.

MAH's responses

According to the protocol, the treatment of a BE was rated by the patient's parent(s)/legal guardian(s) (together with the Investigator in case of on-site treatment) and documented by the investigator in the CRF. Efficacy was to be rated as "none" if there was no improvement within 12 hours, or worsening of symptoms, requiring more than 2 infusions for complete resolution. The 6 bleeding episodes (BEs) with efficacy of *Human-cl rhFVIII* treatment rated as "none".

Summary

The efficacy of *Human-cl rhFVIII* in the treatment of BEs was assessed in the GENA-05 study based on a 4-point ordinal scale and documented by the investigator in the CRF. Efficacy was reported as "none" for 6 BEs, although, for one of these BEs the investigator noted that efficacy could not be assessed as the patient was undergoing ITI treatment. In all cases, these BEs resolved without requiring treatment other than *Human-cl rhFVIII* and the patient continued in the study until completion according to protocol. Other BEs occurring in the patients who had BEs with efficacy reported as "none" were well managed with *Human-cl rhFVIII* treatment, demonstrating the efficacy of *Human-cl rhFVIII* in these patients. Overall, these 6 cases with efficacy rated as "none" do not indicate an overall lack of efficacy for the treatment of BEs with *Human-cl rhFVIII*, especially when considering that treatment with *Human-cl rhFVIII* was rated as "excellent" for 510 BEs, "good" for 237 BEs, and "moderate" for 51 BEs.

Assessment of the MAH's responses

As requested, the MAH provided additional details on the six BEs with an efficacy rating of "none". According to the MAH's response, one of these ratings likely resulted from an inappropriate dosing of *Human-cl rhFVIII* and another one should have been rated as "not available", instead of "none". All of the remaining BEs (4) were ultimately managed with *Human-cl rhFVIII* and resolved without the requirement for other treatments. Furthermore, all patients who had BEs with efficacy reported as "none" experienced additional BEs which were successfully treated with *Human-cl rhFVIII*. Hence, the reported treatments with an efficacy rating of "none" do not change the conclusion of an overall satisfying haemostatic efficacy of *Human-cl rhFVIII* in GENA-05.

Issue ***resolved.***

Question 3

As a result of the type 2 variation EMEA/H/C/002813/II/0017/G, the PT hypersensitivity in the ADR table of the SmPC (section 4.8) covers multiple AEs of allergic symptoms including events of rash and urticaria. Given the at least 12 additional drug-related "allergic" AEs (5 cases of rash, 4 cases of hypersensitivity, 2 cases of urticaria) reported in GENA-05, the MAH should confirm that the frequency category "common" (≥1/100 to <1/10) as specified in the current SmPC for the PT hypersensitivity remains unchanged.

MAH's responses

The existing calculation for the frequency of the PT hypersensitivity already includes the interim data of the GENA-05 study. With the new data from the finalized GENA-05 study the number of patients with ADRs within the PT term "hypersensitivity" changes from 6 of 280 to 8 of 298 and the frequency from

1/46 to 1/37.25. Consequently, it can be confirmed that the frequency category "common" (≥1/100 to <1/10) as specified in the current SmPC for the PT hypersensitivity remains unchanged.

Assessment of the MAH's responses

As requested, the MAH confirmed an unchanged frequency category for the PT "hypersensitivity". The MAH clarified that the underlying frequency calculation already includes interim data of GENA-05. Hence, final data of GENA-05 add only 2 patients with ADRs within the PT "hypersensitivity" to the existing safety database, changing its frequency from 1/46 to 1/37.25.

*Issue **resolved.***

Question 4

Given the 28 additional cases of drug-related pyrexia (plus an additional event of chills) reported in GENA-05, the MAH is requested to confirm that the frequency category "common" (≥1/100 to <1/10) as specified in the current SmPC for the PT pyrexia remains unchanged.

MAH's responses

The existing calculation for the frequency of "pyrexia" already includes the interim data of the GENA-05 study. With the new data from the finalized GENA-05 study, the number of patients with ADRs of "pyrexia" or "chills" changes from 5 of 280 to 22 of 298, and the frequency from 1/56 to 1/13.54. Consequently, it can be confirmed that the frequency category "common" (≥1/100 to <1/10) as specified in the current SmPC for the PT "pyrexia" remains unchanged.

Assessment of the MAH's responses

As requested, the MAH confirmed an unchanged frequency category for the PT "pyrexia". The MAH clarified that the underlying frequency calculation already includes interim data of GENA-05. Hence, final data of GENA-05 add only 17 patients with ADRs within the PT "pyrexia" to the existing safety database, changing its frequency from 1/56 to 1/13.54.

*Issue **resolved.***

Question 5

The exposure and safety information as summarized in the Critical Expert Overview (Tables 4 and 5) neglect data obtained during the final phase of ITI treatment. The ITI addendum to the CSR solely covers data obtained in the ITI sub-study of GENA-05. Hence, it is not clear which of the AEs reported in the final phase of ITI add to the safety data presented in the main CSR (and the Clinical Expert Overview). Thus, the MAH should provide a comprehensive presentation of safety data obtained in GENA-05 (including the ITI sub-study) and, if necessary, update information on potentially drug-related AEs.

MAH's responses

The presentation of safety data in the Critical Expert Overview includes all data obtained in study GENA-05, including the ITI sub-study. This therefore provides an overview of all safety data, including all treatment-related AEs.

Compared to the final GENA-05 CSR, dated 21-June-2019, a further 22 AEs were observed in 5 patients by the time of completion of the ITI sub-study and are included in the Critical Expert Overview and the ITI CSR addendum. These AEs are listed below. One of these AEs was assessed as treatment-

related (FVIII inhibitor [relapse] in one patient and was serious. Most of the AEs were mild or moderate infections, which are expected when monitoring long-term safety in young haemophilia patients.

Patient	MedDRA Preferred Term	Severity	Serious	Treatment	EDs at onset	Outcome	Causality Sponsor
	Diarrhoea	Mild	No	ITI	612	Recovered/Resolved	Not related
	Vomiting	Mild	No	ITI	636	Recovered/Resolved	Not related
	Cough	Moderate	No	ITI	646	Recovered/Resolved	Not related
	Diarrhoea	Moderate	No	ITI	651	Recovered/Resolved	Not related
	Cough	Moderate	No	ITI	682	Recovered/Resolved	Not related
	Bronchitis	Moderate	No	ITI	755	Recovered/Resolved	Not related
	Otitis media	Moderate	No	ITI	Not available	Recovered/Resolved	Not related
	Oral herpes	Mild	No	ITI	876	Recovered/Resolved	Not related
	Nasopharyngitis	Moderate	No	ITI	912	Recovered/Resolved	Not related
	Oral herpes	Mild	No	ITI	934	Recovered/Resolved	Not related
	Nasopharyngitis	Moderate	No	ITI	951	Recovered/Resolved	Not related
	Nasopharyngitis	Moderate	No	ITI	1003	Recovered/Resolved	Not related
	Oral herpes	Mild	No	ITI	1039	Recovered/Resolved	Not related
	Diarrhoea	Mild	No	ITI	1088	Recovered/Resolved	Not related
	Pyrexia	Mild	No	ITI	1089	Recovered/Resolved	Not related
	Rhinorrhoea	Mild	No	ITI	942	Recovered/Resolved	Not related
	Conjunctivitis	Mild	No	ITI	957	Recovered/Resolved	Not related
	Bronchitis	Mild	No	ITI	927	Recovered/Resolved	Not related
	Factor VIII inhibition (relapse)	Mild	Yes	ITI	885	Not recovered/Not resolved	Probable
	Fatigue	Mild	No	ITI	Not available	Recovered/Resolved	Not related
	Ecchymosis	Mild	No	ITI	Not available	Recovered/Resolved	Not related
	Thrombocytopenia	Mild	No	ITI	497	Recovered/Resolved	Not related

ED=Number of days of exposure to *Human-cl rhFVIII*; ITI=immune tolerance induction; MedDRA=Medical Dictionary for Regulatory Activities;

Assessment of the MAH's responses

The MAH clarified that the safety data summarized in the Critical Expert Overview covers all data obtained in GENA-05, i.e. including the final phase of the ITI sub-study. Furthermore, the MAH specified that compared to the final GENA-05 CSR, a further 22 AEs were observed in 5 patients by the time of completion of the ITI sub-study. Of these, only a case of FVIII inhibitor relapse was considered related to the study drug. Hence, the MAH's response does not change the conclusion of an overall acceptable safety profile of *Human-cl rhFVIII* in PUPs.

Issue ***resolved.***

Comment for the MAH:

Minor changes to the SmPC, namely an update of the numbers of evaluated subjects in section 4.8 and removal of the sentence *"A prospective open-label clinical study in PUPs with severe haemophilia A (<1% FVIII:C) is ongoing"* in section 5.1 should be implemented timely with the next revision of the SmPC.

Note: The MAH informed about the plan to update sections 4.8 and 5.1 of the SmPC.

5. CHMP's overall conclusion and recommendation on the responses to requested clarifications

In summary, data obtained in previously untreated patients (PUPs) in GENA-05 do not change the favourable benefit risk profile of *Human-cl rhFVIII* in pediatric patients. The MAH provided appropriate responses to requests for supplementary information. The presented data do not warrant any update of the Product information and no regulatory actions are required.

☒ **Fulfilled, no further action required.**

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

Non-clinical studies

Study title	Study number	Date of completion	Date of submission of final study report
Recombinant Human Factor VIII (rhFVIII): Single Dose Toxicity Study by Intravenous Injection to CD Rats (GLP)	DWL 0003/063496	21-Sept-2006	29-May-2013
Cross-over Comparative Study of the Efficacy and Pharmacokinetics of a novel B Domaindeleted Recombinant Coagulation Factor VIII Concentrate in a Canine Model of Hemophilia A (non-GLP)	- (internally referred to as "Oct 10 2007")	10-Oct-2007	29-May-2013
Recombinant Human Factor VIII (rhFVIII): Local Tolerance Study in the Rabbit following Perivenous injection (GLP)	DWL 0004/073723	19-Feb-2008	29-May-2013
Recombinant Human Factor VIII (rhFVIII): Toxicity Study by Intravenous Administration to Cynomolgus Monkeys for 4 weeks followed by a 2 week recovery period (GLP)	DWL 0002/064067	23-May-2008	29-May-2013
Recombinant Human Factor VIII (rhFVIII): Preliminary Toxicity Study by Intravenous Bolus Injection to Cynomolgus Monkeys (GLP)	DWL 0001/063743	27-May-2008	29-May-2013
EpiScreen™ T Cell Epitope Mapping of Factor VIII Linker Sequences (non-GLP)	OCT01	11-Mar-2010	29-May-2013
EpiScreen™ Study 2 Immunogenicity Testing VWF Pre-Screen Study (non-GLP)	Pre-screen: OCT01 Study 2	22-Nov-2010	29-May-2013
Pharmacokinetics of Human-cl rhFVIII in Hemophilia Dogs (Octapharma summary report)	OC11-0200	08-Jul-2011	29-May-2013
EpiScreen™ Study 2 Immunogenicity Testing of Vivante Isoforms with von Willebrand Factor (non-GLP)	OCT02 Study 4	17-Nov-2011	29-May-2013
EpiScreen™ Study 2 Immunogenicity Testing of Factor VIII Products with von Willebrand Factor (non-GLP)	OCT01 Study 2	16-Nov-2012	29-May-2013
Local Tolerance Study of Four Nuwiq® Strengths following a single perivenous Administration in Rabbits ´(GLP)	LPT 33166	18-Apr-2016	27-Apr-2017

Clinical studies

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

viously Treated Patients with Severe Haemophilia A				
Prospective Clinical Study in Children with Severe Haemophilia A to Investigate Clinical Efficacy, Immunogenicity, Pharmacokinetics, and Safety of Human-cl rhFVIII	GENA-03[1]	2010-018644-14	15-Feb-2013	29-May-2013
Clinical Study in Previously Treated Children with Severe Haemophilia A to Investigate the Long-Term Immunogenicity, Tolerability and Efficacy of Human-cl rhFVIII	GENA-13	2011-001785-17	22-Nov-2016	07-Dec-2016
Clinical Study to Investigate the Pharmacokinetics, Efficacy, Safety and Immunogenicity of Human-cl rhFVIII in Previously Treated Patients with Severe Haemophilia A	GENA-09[2]	2008-006172-29	14-Dec-2010	29-May-2013
Clinical Study to Investigate the Long-Term Safety and Efficacy of Human-cl rhFVIII in Previously Treated Patients with Severe Haemophilia A	GENA-04[2]	2009-014422-41	22-Mar-2012	29-May-2013
Immunogenicity, Efficacy and Safety of Treatment with Human-cl rhFVIII in Previously Untreated Patients with Severe Haemophilia A	GENA-05[1]	2012-002554-23	Ongoing	Not applicable
Extension Study for Patients who Completed GENA-05 (NuProtect) – to Investigate Immunogenicity, Efficacy and Safety of Treatment with Human-cl rhFVIII	GENA-15	2013-003997-28	16-Sep-2019	Current submission
Prospective, Open-Label, Multicentre Phase 3b Study to Assess the Efficacy and Safety of Individually Tailored Prophylaxis with Human-cl rhFVIII in Previously Treated Adult Patients with Severe Haemophilia A	GENA-21	2013-001556-35	13-Jan-2016	26-Sep-2018
Prospective, Open-Label, Multicentre Phase 3b Study to Assess the Efficacy and Safety of Personalized Prophylaxis with Human-cl rhFVIII in Previously Treated Adult Patients with Severe Haemophilia A	GENA-21b	2014-002986-30	Ongoing	Not applicable
Prospective clinical study to investigate the clinical efficacy, immunogenicity, pharmacokinetics and safety of Human-cl rhFVIII in Chinese patients with severe haemophilia A	GENA-40	Not applicable	Ongoing	Not applicable

[1], pivotal study for obtaining marketing authorization
[2], supportive study for obtaining marketing authorization