Amsterdam, 12 November 2020
EMA/CHMP/692798/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Nuwiq / Vihuma

International non-proprietary name: simoctocog alfa

Procedure no.: EMEA/H/C/002813/P46 013 & EMEA/H/C/004459/P46 012

Note

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

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1. Introduction

On 3rd July 2020, the MAH submitted a completed paediatric study (GENA-40) for Nuwiq/Vihuma, in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended. At that time, only a summary study report was provided in order to meet the submission deadline of 6 months after study completion. Since the final study report was expected for October 2020, it was decided to await the full final study report prior to scientific review. As a consequence and in accordance with the EMA submission requirements for Article 46 paediatric studies, the following issues were raised (RSI sent 11 August 2020):

1. The final clinical study report of GENA-40 has to be submitted (announced for October 2020).
2. A critical clinical overview has to be submitted

In response, the MAH submitted the full study report of GENA-40 on 02 October 2020. Concerning the requested critical clinical overview document, the MAH referred to the Critical Expert Overview submitted together with the final clinical study report of GENA-05 (submitted according to Art. 46 of Regulation (EC) No 1901/2006 on 24 September 2020) combining the information on both studies (GENA-05 and GENA-40) in one report.

As stated in the original Cover Letter, dated 03 July 2020, no amendments to be introduced to the Product Information, and thus no regulatory consequences, have been identified by the MAH.

2. Scientific discussion

2.1. 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-40) has been conducted as part of the clinical development program of *Human-cl rhFVIII*, with the rationale of subsequently applying for the approval of *Human-cl rhFVIII* in China. A line listing of all non-clinical and clinical studies which are part of the development programme of *Human-cl rhFVIII* is annexed to this report.

2.2. 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.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- GENA-40: Prospective clinical study to investigate the clinical efficacy, immunogenicity, pharmacokinetics and safety of *Human-cl rhFVIII* in Chinese patients with severe haemophilia A

2.3.2. Clinical study

Clinical study number and title

GENA-40: Prospective clinical study to investigate the clinical efficacy, immunogenicity, pharmacokinetics and safety of Human-cl rhFVIII in Chinese patients with severe haemophilia A

Description

GENA-40 was a prospective, non-controlled, open-label, multinational, multicentre Phase 3b study of 63 PTPs (≥6 years) with severe haemophilia A with at least 150 previous EDs to FVIII concentrates. The study was conducted exclusively in Chinese patients, both children and adults. GENA-40 included 24 children between 6 and 12 years of age and 15 adolescents. Patients received treatment with *Human-cl rhFVIII* for a period of 6 months. The study was initiated in June 2018 and completed in January 2020.

Methods

Objective(s)

Primary:

The primary objective of the study was to assess the clinical efficacy of *Human-cl rhFVIII* in the prevention and treatment of bleeding episodes (BEs).

Secondary:

- To determine the pharmacokinetic (PK) profile of *Human-cl rhFVIII* by measurement of the area under the curve (AUC), half-life ($T_{1/2}$), incremental in-vivo recovery (IVR), maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), mean residence time (MRT), volume of distribution at steady state (V_{ss}) and clearance (CL);
- To determine the IVR of *Human-cl rhFVIII* – at study start and over time;
- To investigate the immunogenic potential of *Human-cl rhFVIII* by assessing inhibitor titre;
- To assess the efficacy of *Human-cl rhFVIII* as surgical prophylaxis;
- To assess the safety of *Human-cl rhFVIII* by monitoring adverse events (AEs).

Study design

GENA-40 was a prospective, non-controlled, open-label, multinational, multicentre Phase 3b study, planned to be performed in 60 evaluable male Chinese PTPs (≥6 years) with severe haemophilia A (FVIII:C <1%). Around 12 centres in China were planned to participate in this study. The study comprised a PK assessment of *Human-cl rhFVIII* in a subgroup of 20 patients (restricted to patients ≥12 years) and a 6-Month treatment period with *Human-cl rhFVIII*. For the evaluation of PK, patients received a single dose of *Human-cl rhFVIII* (50±5 IU FVIII/kg). During the 6-Month treatment period,

patients were treated with *Human-cl rhFVIII* either prophylactically or on demand. The main focus of the study was the investigation of the clinical efficacy of *Human-cl rhFVIII* in the prevention and treatment of BEs. In addition, PK parameters, IVR over time, immunogenicity and safety were assessed. If patients underwent surgery during the study, the efficacy of surgical prophylaxis was documented.

Study population /Sample size

GENA-40 was conducted exclusively in Chinese patients, both children and adults. The study was open to male Chinese patients ≥6 years of age with severe haemophilia A who were previously treated with FVIII concentrate for at least 150 exposure days (EDs). The study was planned to enroll approximately 70 patients (60 evaluable patients), 20 of whom were to undergo an initial PK assessment (PK subgroup). Sample size was chosen based on publications from other haemophilia A studies conducted in China for licensure of rFVIII products.

Treatments

For the 6-Month Treatment Period, prophylactic treatment was recommended, but it was ultimately the decision of the responsible treating physician whether patients were treated prophylactically or on demand.

Prophylactic Treatment:

Patients were to receive 30–40 IU FVIII/kg BW of *Human-cl rhFVIII* every-other-day or three-times-weekly for 6 months. Two dose escalations of +5 IU FVIII/kg BW each were to be implemented in case of an inadequate response (>2 spontaneous BEs within one month). In cases of inadequate response, *Human-cl rhFVIII* administration frequency or dose adjustments were to be considered at the Investigator's discretion.

On-Demand Treatment:

Patients could receive *Human-cl rhFVIII* for the treatment of breakthrough BEs during prophylaxis or as on-demand only treatment. The dosage and duration of treatment of spontaneous or traumatic BEs depended on the location and the extent of the BE as well as on the clinical situation of the patient. Dosage recommendations were provided as follows:

- Minor BEs: 20–30 IU FVIII/kg BW every 12–24 hours until BE is resolved;
- Moderate to major BEs: 30–40 IU FVIII/kg BW. Repeat dose every 12–24 hours until BE is resolved;
- Major to life threatening BEs: Initial dose of 50–60 IU FVIII/kg BW. Repeat dose of 20–25 IU FVIII/kg BW every 8–12 hours until BE is resolved.

Surgical Prophylaxis:

The dosage and duration of treatment with *Human-cl rhFVIII* depended on the type of surgery. Dosage recommendations were provided as follows:

- Minor surgeries including tooth extractions: 25–30 IU FVIII/kg BW within 3 hours prior to surgery to achieve an intended target peak level of approximately 50–60%. Repeat one dose at 12–24 hours if needed. Trough level should be maintained at approximately 30%;
- Major surgeries: 50 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 ≥6 days until healing is complete. Trough level should be maintained at approximately 50%.

Outcomes/endpoints

Primary:

- Efficacy: The clinical efficacy of *Human-cl rhFVIII* in the prevention and treatment of BEs was assessed during the 6-Month treatment period. The efficacy of *Human-cl rhFVIII* in prophylactic treatment was evaluated as excellent, good, moderate, or poor based on the frequency of spontaneous BEs per month. The analysis of *Human-cl rhFVIII* in prophylactic treatment was further analysed based on the annualized bleeding rate (ABR) for spontaneous breakthrough bleeds; this was not planned in the protocol but was added in the statistical analysis plan.

  The efficacy of *Human-cl rhFVIII* in the treatment of BEs (breakthrough BEs during prophylaxis and BEs during on-demand treatment) was assessed on a 4-point scale as excellent, good, moderate or none. Details of the BE (type, site and severity of the BE, and the start and end date and time of the BE), the amount of *Human-cl rhFVIII* needed and the number of injections necessary to stop the BE were documented.

Secondary:

- PK Parameters: A full PK analysis using a non-compartmental model was performed with *Human-cl rhFVIII* (50±5 IU FVIII/kg BW) in the PK subgroup at study start. The following PK parameters were assessed: AUC, $T_{1/2}$, IVR, C_{max}, T_{max}, MRT, V_{ss} and CL. PK parameters for *Human-cl rhFVIII* were calculated using the labelled and actual potency and actual sampling time points. FVIII:C was measured with the one-stage assay at the central laboratory in China.
- IVR: IVR investigations for *Human-cl rhFVIII* (50±5 IU FVIII/kg BW) were conducted at study start and after 3 and 6 months of treatment with *Human-cl rhFVIII*. Sampling time points were at baseline (prior to infusion) and at 30 minutes and 1 hour (±5 minutes) post infusion. Actual time points were documented. IVR for *Human-cl rhFVIII* was calculated using the labelled and actual potency and actual sampling time points. FVIII:C was measured with the one-stage assay at the central laboratory in China. IVR over time was analysed.
- Immunogenicity: Inhibitor activity was determined by the modified Bethesda assay (Nijmegen modification), using congenital FVIII-deficient human plasma spiked with *Human-cl rhFVIII* at Screening the ED 10–15 visit, the 3 months visit (±2 weeks); and at 6 months / study completion visit (+2 weeks); and at any time in the case of a suspicion of inhibitor development. In case of a positive inhibitor result, an inhibitor re-test of a second separately drawn sample was to be performed. Samples were analysed at the central laboratory in China.
- Surgery: Efficacy was assessed at the end of surgery by the surgeon and post-operatively by the haematologist using pre-defined scales. An overall efficacy assessment, taking both the intra- and post-operative assessment into account, was performed jointly by the surgeon and the haematologist using an algorithm as guidance.
- Safety: Clinical safety was assessed by monitoring AEs throughout the study, and by physical examination, vital signs, and safety laboratory parameters at pre-defined time points.

Statistical Methods

The primary approach to the statistical analysis was descriptive, presenting summary tables for the measured and derived variables. No inferential analysis involving formal testing was planned in this non-controlled trial.

Results

Recruitment/ Number analysed

A total of 63 Chinese patients, all previously treated patients (PTPs), were enrolled and treated with *Human-cl rhFVIII* at 11 investigational centres in China. 62 patients completed the study. One patient discontinued prematurely due to low compliance. All 63 enrolled patients were treated prophylactically and included into the SAF, ITT, and PROPH populations. No patients were treated only on-demand.

Baseline data

Age at screening ranged from 6 to 51 years, with a median of 15 years. All patients were Asian. The study population included 24 children between 6 and 12 years of age (median: 8 years, range: 6-11 years) and 15 adolescents (median: 15 years, range: 12-17 years). In the group of 6 - <12 years and 12 - <18 years, median HJHS at screening was 4 (range, 0-28) and 6 (range, 0-27), respectively.

Efficacy results

PK evaluation:

PK was assessed in a subgroup of 20 patients ≥12 years of age. Of these, 7 patients were aged 12 - <18 years and 13 were aged ≥18 years. The concentration-time profile was consistent with the well-characterized profile for *Human-cl rhFVIII* in previous studies: mean concentrations were increased at 30 minutes post-injection and remained elevated compared with baseline values at 60 minutes post-injection, although a slight decrease in mean concentrations was observed between 30 and 60 minutes due to elimination of the infused FVIII, and by 48 hours post-injection, concentrations had decreased to levels slightly above pre-injection levels. The concentration-time profiles reflected slightly lower recovery for patients aged 12 - <18 years compared to patients ≥18 years. Summary statistics for the PK parameters of *Human-cl rhFVIII*, using calculations based on the actual relative dose, are provided for the one stage assay in Table 1 below. The observed mean (±SD) half-life of 10.2 ± 1.3 hours was at the lower end compared to that reported in other studies with *Human-cl rhFVIII* (e.g. 17.1±11.2 in GENA-01, 12.5±4.2 in GENA-03 and 11.4±3.9 in GENA-09) and, correspondingly, the observed mean (±SD) AUC_{norm} of 0.18 ± 1.4 h·IU/mL/[IU/kg] was lower than that reported in other studies with *Human-cl rhFVIII* (e.g. 0.37±0.11 in GENA-01, 0.24±0.08 in GENA-03 and 0.29±0.13 in GENA-09). PK parameters were broadly comparable between the adolescent and adult age groups, with slightly higher C_{max} and AUC_{norm} observed in the adult age group.

Table 1: Statistics on PK parameters obtained in GENA-40

Parameter/group	n	Mean	SD	CV (%)	Median	Range
C_{max} (IU/mL)						
Total	20	0.883	1.3536	21.658	0.855	0.57-1.55
12 - <18 yrs	7	0.787	1.3195	19.792	0.733	0.59-1.39
≥18 yrs	13	0.940	1.3604	22.023	0.950	0.57-1.55
In-vivo recovery (kg/dL)						
Total	20	1.690	1.3523	21.587	1.582	1.12-3.08
12 - <18 yrs	7	1.514	1.3120	19.378	1.434	1.13-2.62
≥18 yrs	13	1.794	1.3642	22.230	1.788	1.12-3.08
AUC∞ (h*IU/mL)						
Total	20	9.125	1.4247	25.425	9.441	5.18-16.82
12 - <18 yrs	7	8.484	1.4407	26.252	8.509	5.20-16.82
≥18 yrs	13	9.489	1.4280	25.600	10.050	5.18-16.31
AUC_{norm} (h*kg*IU/mL/IU)						
Total	20	0.177	1.4177	25.063	0.181	0.10-0.34
12 - <18 yrs	7	0.165	1.4434	26.392	0.164	0.10-0.34
≥18 yrs	13	0.184	1.4166	25.002	0.199	0.11-0.30
AUMC∞ (hr*IU/mL)						
Total	20	125.121	1.7582	41.544	123.681	46.92-357.17
12 - <18 yrs	7	116.461	1.5446	31.482	126.829	60.07-244.02
≥18 yrs	13	130.047	1.8897	47.381	120.533	46.92-357.17
$T_{1/2}$						
Total	20	10.226	1.2962	18.498	9.613	6.30-17.98
12 - <18 yrs	7	10.352	1.1444	9.557	10.223	8.39-12.52
≥18 yrs	13	10.159	1.3661	22.330	8.982	6.30-17.98
CL (mL/hr/kg)						
Total	20	5.653	1.4177	25.063	5.515	2.98-9.60
12 - <18 yrs	7	6.059	1.4433	26.390	6.098	2.98-9.60
≥18 yrs	13	5.446	1.4166	25.004	5.027	3.33-9.53
MRT (h)						
Total	20	13.712	1.3474	21.322	13.274	7.74-27.40
12 - <18 yrs	7	13.726	1.1341	8.918	14.511	11.54-15.46
≥18 yrs	13	13.705	1.4398	26.209	11.782	7.74-27.40
V_{ss} (mL/kg)						
Total	20	77.522	1.3921	23.714	81.099	43.19-151.52
12 - <18 yrs	7	83.171	1.3956	23.900	90.891	43.19-17.64
≥18 yrs	13	74.641	1.4001	24.138	64.812	45.19-151.52

AUC = area under the curve (from baseline to infinity); AUC_{norm} = AUC divided by the dose; AUCM = area under the moment curve; CI = confidence interval; CL = clearance; C_{max} = maximum plasma concentration; CV = coefficient of variation; IU = international unit; SD = standard deviation; MRT = mean residence time; $T_{1/2}$ = half-life; T_{max} = time to reach maximum plasma concentration; V_{ss} = volume of distribution at steady state; yrs = years.

Source: Table 25, CSR

A total of 63 patients were included in the ITT population and were evaluable for IVR assessment. Results of the IVR analyses are summarized in Table 2 below. Mean IVR values were consistently 1.8%/IU/kg at ED1, 3 months and 6 months. The mean IVR values were slightly lower for the 6 - <12 years and 12 - <18 years age groups, but were >1.6%/IU/kg at each time point.

Table 2: IVR (%/IU/kg) in the ITT population of GNEA-40 based on actual dose administered

Group Time point	n	Mean	SD	Median	Range
Total, ED1	63	1.79	0.579	1.63	0.85-3.72
Total, 3 months	63	1.85	0.581	1.69	0.91-3.67
Total, 6 months	63	1.85	0.644	1.77	0.88-5.20
6 - <12 yrs, ED1	24	1.60	0.546	1.48	0.85-3.72
6 - <12 yrs, 3 months	24	1.69	0.550	1.57	0.91-2.97
6 - <12 yrs, 6 months	24	1.72	0.834	1.53	0.88-5.20
12 - <18 yrs, ED1	15	1.72	0.631	1.44	1.13-3.16
12 - <18 yrs, 3 months	15	1.74	0.497	1.55	1.10-2.59
12 - <18 yrs, 6 months	15	1.83	0.463	1.80	1.23-2.70
≥18 yrs, ED1	24	2.02	0.528	2.08	1.14-3.01
≥18 yrs, 3 months	24	2.08	0.606	2.00	1.10-3.67
≥18 yrs, 6 months	24	1.99	0.506	2.02	1.19-3.07

ED = exposure day; SD = standard deviation, yrs = years.

Source: Table 28, CSR

Prophylactic treatment:

In GENA-40, all patients received prophylactic treatment with *Human-cl rhFVIII*. The planned dosing regimen was three-times-weekly in 55 (87.3%) patients and every-other-day in 8 (12.7%) patients. The mean duration of prophylactic treatment was 6.1 months, ranging from 4 to 6.5 months. The mean dose (±SD) per kg per ED for prophylaxis was 35.0 ± 2.7 IU/kg/ED (median: 35.1 IU/kg; range, 29–40). There were no relevant differences between the age groups. The mean (±SD) monthly doses of *Human-cl rhFVIII* were 426.7 ± 52.1 IU/kg in 6 - <12 year old children, 422.0 ± 43.4 IU/kg in adolescents, and 449.1 ± 43.4 IU/kg in adults.

Under prophylaxis, 77.7% of the patients ihad 0 to 3 BEs under prophylaxis including 19 patients without any BE during treatment. The monthly rate of spontaneous break-through bleeds (MBR) during time of prophylactic treatment was assessed as excellent, good, moderate or poor. The efficacy of prophylactic treatment was excellent (MBR <0.75) in 60 patients (95.2%), good (MBR 0.75–1) in 1 (1.6%) patient, and poor (MBR >1.5) in 2 (3.2%) patients. The patients with efficacy rated as 'poor' were two adolescents, of whom one discontinued prematurely due to low compliance (MBR of 4.31) and the other did not receive treatment according to protocol (MBR of 1.60).

The spontaneous, traumatic, and overall annualized bleeding rates (ABRs) in total and by age group are summarized in Table 3 below. In the per-protocol population the median ABRs (IQR) for all BEs were 1.94 (1.87, 3.90) in 6-<12 year old children (n=20), 2.05 (0.95, 4.88) in adolescents (n=12), and 1.89 (0, 5.77) in adults (n=21).

Table 3: Annualized bleeding rates during prophylactic treatment

	Mean	SD	Median	Range	IQR
ABR, spontaneous BEs					
6–<12 years (n=24)	2.02	2.678	1.92	0-11.9	0-2.87
12–<18 years (n=15)	6.16	13.518	1.97	0-51.8	0-3.89
≥18 years (n=24)	1.39	2.252	0.00	0-7.42	0-2.90
Total (n=63)	2.77	7.038	0.00	0-51.8	0-3.82
ABR, traumatic BEs					
6–<12 years (n=24)	2.76	4.594	0.94	0-15.5	0-1.93
12–<18 years (n=15)	1.92	2.172	1.89	0-5.8	0-3.84
≥18 years (n=24)	2.62	4.242	0.93	0-15.9	0-3.16
Total (n=63)	2.51	3.960	1.85	0-15.9	0-3.84
ABR, all BEs					
6–<12 years (n=24)	4.94	5.695	2.89	0-21.4	1.87-6.96
12–<18 years (n=15)	8.08	13.452	3.84	0-51.8	1.89-7.77
≥18 years (n=24)	5.06	7.873	1.93	0-31.4	0-5.99
Total (n=63)	5.74	8.811	2.12	0-51.8	0-5.99

For "other" and "missing" bleed types, refer to the source table. There were no postoperative bleeds.
ABR = annualized bleeding rate, BE = bleeding episode, IQR = interquartile range, PROPH = study population of patients receiving prophylaxis, SD = standard deviation

Source: Table 17, CSR

Treatment of bleeding episodes:

The number of treated treatment-emergent BEs was 173. Of these, 81 (46.8%) were documented as spontaneous, 78 (45.1%) as traumatic, 13 (7.5%) as 'other', and 1 (0.6%) had missing type. BEs where the site was specified were most common in the ankle (53 [30.6%]), knee (23 [13.3%]), and elbow (22 [12.7%]). 'Other' sites of bleeding were mainly BEs characterized by multiple sites and accounted for 39 (22.5%) BEs. The efficacy assessment of bleeding episodes at end of a BE was evaluated on an objective 4-point scale by the patient/legal guardian (together with the Investigator in case of on-site treatment). The patient/Investigator rated the majority of BEs as having excellent (60.7%) or good (19.1%) treatment efficacy, giving a success rate of 79.8%; treatment efficacy was rated as moderate for 18.5% of BEs. The sponsor also performed a post-hoc assessment, based on the number of infusions needed to stop the bleed and the bleeding duration, re-evaluating BEs that appeared to not have been rated in-line with the rating scale and BEs with no rating. More BEs were rated as having excellent efficacy by the sponsor as compared to the patient/Investigator (69.4% vs. 60.7%) but the overall success rate remained comparable (80.9% vs. 79.8%); 9 (5.2%) BEs were rated by the sponsor as having an efficacy assessment of 'none' as 5 infusions were administered and duration of bleeding episode was ≥72 hours.

In the group of paediatrics, a total of 31 children (N=19 between 6 and <12 years, N=12 between 12 to <18 year) experienced a total of 114 BEs (N=61 in the group of 6-<12 year olds, N=53 in the group

of 12-<18 year olds) that were treated with *Human-cl rhFVIII*. None of these BEs was a major bleeding episode. Results of the sponsor's efficacy assessment for the treatment of BEs by age group are summarized in Table 3 below.

Table 4: Overall efficacy assessment for bleeding episodes

Efficacy Assessment per Bleeding Episode	Age class (Years)						Total	
	6 - <12 (Children)		12 - <18 (Adolescents)		>=18 (Adults)			
	n	%	n	%	n	%	n	%
Excellent	46	75.41	29	54.72	45	76.27	120	69.36
Good	4	6.56	12	22.64	4	6.78	20	11.56
Moderate	8	13.11	7	13.21	8	13.56	23	13.29
None	3	4.92	5	9.43	1	1.69	9	5.20
Missing	0	0.00	0	0.00	1	1.69	1	0.58
Total	61	100.00	53	100.00	59	100.00	173	100.00

Source: Table 14.2.2.5-1, CSR

Most BEs (141 [81.5%]) were resolved with 1 (121 BEs) or 2 (20 BEs) infusions of *Human-cl rhFVIII*. The median number of infusions per BE was 1.0 (IQR: 1.00, 2.00; range: 0-110), and the median dose per episode/kg body weight was 35.71 IU/kg (IQR: 31.25, 71.43; range: 22.9-4036.6). The number of infusions per BE and the dose per BE/kg body weight were comparable across the age groups (i.e. median doses per BE were 35.71 IU/kg [IQR: 31.25, 51.47; range: 26.7-4036.6] in 6 - <12 year old children and 50.38 IU/kg [IQR: 35.71, 83.33; range: 22.94-520] in the group of adolescents).

Surgical prophylaxis:

In GENA-40, a total of 5 patients had 6 surgeries that were included in the SURG population. One of these surgeries was minor and 5 were major. Four out of 6 surgeries (all major) had an overall efficacy assessment performed jointly by the haematologist and surgeon, all rated as having excellent efficacy. These procedures included a major procedure (i.e. release of right gastrocnemius aponeurosis + lengthening of right Achilles tendon) performed in a 15 year old boy. This patient received one infusion of *Human-cl rhFVIII* before (40 IU/kg) and 23 infusions (15 EDs with an average dose of 51.33 IU/kg per ED) after the procedure (total dose: 2000 + 38500 IU). One minor surgery (tooth extraction in an 8 year old boy) and 1 major surgery (nasal sinus mass removal in an adult) were not assessed due to the procedures having taken place outside of the study site.

Safety results

In GENA-40, patients had a mean of 86 days of exposure to *Human-cl rhFVIII*, received a mean of 91 infusions and a mean dose per kg BW per ED of 36.5 IU/kg/ED. Dosing and exposure were comparable across the age groups. A total of 37 (58.7%) patients experienced 74 treatment-emergent adverse events (AEs). Of the 63 patients in the safety population (SAF), 29 (46.0%) experienced only mild AEs, 7 (11.1%) experienced moderate AEs, and 1 (1.6%) patient experienced a severe AE (pyrexia).

Considering the relatively small sample sizes of the subgroups, there was no clinically relevant difference in the safety profile observed in children, adolescents, and adults. Most AE preferred terms were reported only once. The most commonly reported AEs were upper respiratory tract infection (12 [19.0%] patients), nasopharyngitis (7 [11.1%]), cough (4 [6.3%]), and pyrexia (3 [4.8%]). Pyrexia is an expected adverse reaction for *Human-cl rhFVIII*; however, each AE of pyrexia was assessed as not related to IMP by the investigator. No safety concerns were raised by clinical laboratory, vital sign, and physical examination findings.

There were no deaths in this study. No patient tested positive for FVIII inhibitors. No patients had AEs leading to permanent discontinuation from the study and no AEs were assessed as possibly/probably related to IMP by the Investigators or the sponsor.

2.3.3. Discussion on clinical aspects

As part of this Article 46 procedure, the MAH submitted the final study report of GENA-40 together with an updated Critical Expert Overview. The aim of this Phase 3b study was to assess the efficacy, immunogenicity, PK parameters and safety of *Human-cl rhFVIII* in Asian patients with severe haemophilia A with the rationale of subsequently applying for the approval of *Human-cl rhFVIII* in China. In GENA-40, data was collected from a total of 63 previously treated patients, including 39 children (i.e. 24 children between 6-<12 year of age and 15 adolescents) at 11 investigational centres in China.

The evaluation of clinical efficacy included assessments of haemostatic efficacy of *Human-cl rhFVIII* in routine and surgical prophylaxis and in the treatment of bleeding episodes. Treatment recommendations were comparable to previous trials and generally in line with the posology of *Human-cl rhFVIII* as reflected in the current EU SmPC. Similarly, measurements and assessments employed in GENA-40 were consistent with previous trials conducted in non-Asian patients.

Pharmacokinetic evaluation

In GENA-40, a full PK analysis of *Human-cl rhFVIII* was performed in a subgroup of 20 patients ≥12 years of age, including 7 adolescents. In contrast to the recommendations given in the EMA guideline on the clinical investigation of Factor VIII products (EMA/CHMP/BPWP/144533/2009), the duration of Factor VIII wash-out was ≥72 hours (instead of at least 4 days), patients were not re-tested after 3-6 months, and FVIII:C levels were solely measured with the one-stage clotting assay. With regard to the latter, it is noted that previous studies with *Human-cl rhFVIII* did not indicate significant differences between the one-stage and chromogenic assays.

PK parameters obtained for the group of adolescents were broadly comparable to adults, with slightly higher C_{max} and AUC_{norm} observed in the adult age group. Compared to previous trials conducted in non-Asian patients, results of GENA-40 indicate a trend towards shorter half-life (i.e. 10.2±1.3 hours vs. 17.1±11.2 in GENA-01, 12.5±4.2 in GENA-03 and 11.4±3.9 in GENA-09), lower AUC_{norm} (i.e. 0.18±1.4 h·IU/mL/[IU/kg] vs. 0.37±0.11 in GENA-01, 0.24±0.08 in GENA-03 and 0.29±0.13 in GENA-09) and increased clearance.

In addition to the full PK evaluation, IVR was analysed for all patients at the start and after 3 and 6 months of treatment. As expected and consistent with other products of this class, IVR values were lower in children <12 years of age (i.e. ~1.6%/IU/kg at all time points) compared to adults (~2%/IU/kg at all time points). Again, however, values obtained in the Chinese population were consistently lower than the ones obtained in previous trials as specified in section 5.2 of the EU SmPC (i.e. 1.9%/IU/kg in children aged 6 to 12 years and 2.5%/IU/kg in adults).

While the seeming trend towards lower IVR and overall increased metabolism of *Human-cl rhFVIII* in Chinese patients may be explained by a combination of intrinsic and extrinsic differences between the European and Asian populations, the only small number of patients evaluated in GENA-40 precludes drawing definitive conclusions with regard to the relative impacts of potential ethnicity-related effects and other confounders (e.g. age). With regard to the clinical relevance of potential ethnic differences in the PK behaviour of *Human-cl rhFVIII*, it is noted that results of GENA-40 do not indicate reduced haemostatic efficacy of *Human-cl rhFVIII* in the Chinese patients under study. However, results have to be looked at in the context of rather conservative recommendations for prophylactic dosing in GENA-40 (i.e. 30-40 IU/kg every other day or 3-times weekly). Consequently, potential ethnic differences may become more relevant when comparing less conservative dosing regimens.

Haemostatic efficacy in prophylaxis and in the treatment of BEs

In the paediatric subgroup included in GENA-40, average doses of *Human-cl rhFVIII* administered per prophylactic infusion (i.e. median: 34.9 IU/kg in 6 - <12 year old children and 35.69 IU/kg in adolescents) or for the treatment of BEs (i.e. median: 35.71 IU/kg in 6 - <12 year old children and 50.38 IU/kg in adolescents) were largely comparable to previous trials in paediatric PTPs.

For prophylaxis, mean monthly doses of 426.7 IU/kg in the group of 6 - <12 year old children and 422.0 IU/kg in adolescents compare to a monthly consumption of 531.2 IU/kg reported in the long-term paediatric extension study GENA-13 with similar recommendations regarding prophylactic treatment (i.e. 30-40 IU/kg every other day or 3-times weekly).

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).

Huge ranges in the number of infusions (i.e. 0-110 per BE) and total doses administered to treat BEs (i.e. 22.9-4036.6 IU/kg per BE) were primarily attributed to a single bleeding event in a 11-year old boy (a spontaneous moderate joint bleed in the right knee) for which the patient received a total of 110 infusions over a period of 59 days. Of note, however, according to Listing 16.2.6.3-2, this patient had another traumatic moderate joint bleed that was successfully treated with only 2 infusions and these two BEs remained the only bleeding complications over a period of 6.21 months of prophylaxis indicating overall satisfactory efficacy.

In GENA-40, all patients received prophylaxis for a mean duration of 6.1 months (range: 4-6.5 months). On average, reported annualized bleeding rates are considered largely comparable to previous paediatric trials. Median ABR (IQR) was 2.89 (1.87-6.96) and 3.84 (1.89-7.77) in 6 - <12 year old children and adolescents, respectively. Monthly rates of >1 spontaneous bleeds (MBR) were limited to two adolescents; of whom one discontinued prematurely due to low compliance and the other did not receive treatment according to protocol. In the per-protocol population the median ABRs (IQR) for all BEs were 1.94 (1.87, 3.90) in 6 - <12 year old children (n=20) and 2.05 (0.95, 4.88) in the group of adolescents (n=12). Of note, these numbers have to be generally interpreted in the context of highly vulnerable population under study (i.e. children <12 years of age and adolescents), prone to trauma-induced bleeding and/or non-compliance. The only surgical procedure with available assessment in the paediatric population (i.e. release of right gastrocnemius aponeurosis + lengthening of right Achilles tendon in a 15 year old boy) was rated as having excellent efficacy.

Hence, overall, it is concluded that results of GENA-40 essentially confirm haemostatic efficacy of *Human-cl rhFVIII* in the Asian population without indicating relevant differences compared to non-Asian patients.

Safety data

Safety data obtained in GENA-40 are considered consistent with previous experiences and do not indicate any safety issues specific to the Asian or Asian paediatric populations. Neither types nor frequencies of reported TEAEs are considered remarkable. None of the patients included in GENA-40 developed FVIII inhibitors and there were no reports of thromboembolic events. The only case of treatment-emerged hypersensitivity occurred in a 43-year old patient and was considered not related to the study drug. Of note, this patient had already receive 45 EDs with Human-cl rhFVII before the onset of this AE and went on to complete the study with 80 EDs without recurrence of allergic symptoms. Although limited by the only small sample sizes of the different age groups, data from GENA-40 do not indicate any clinically relevant differences with regard to the safety profile of *Human-cl rhFVIII* in children, adolescents, and adults. Overall, *Human-cl rhFVIII* was well tolerated and none of the reported AEs were assessed as possibly/probably related to the administration of *Human-cl rhFVIII*.

3. Rapporteur's initial overall conclusion and recommendation

☒ **Not fulfilled:**

Based on the data submitted, the MAH should is requested provide the final clinical study report of GENA-40 and a critical clinical overview as part of this procedure. (see section "Additional clarification requested")

4. Initial clarification requested

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

3. The final clinical study report of GENA-40 has to be submitted (announced for October 2020).
4. A critical clinical overview has to be submitted.

The timetable should be a **60 day response timetable**, since the final report has been not submitted within the initial submission.

5. MAH responses to initial clarification request

The MAH submitted the full study report of GENA-40 on 02 October 2020. Concerning the requested critical clinical overview document, the MAH referred to the Critical Expert Overview submitted together with the final clinical study report of GENA-05 (submitted according to Art. 46 of Regulation (EC) No 1901/2006 on 24 September 2020) combining the information on both studies (GENA-05 and GENA-40) in one report.

As stated in the original Cover Letter, dated 03 July 2020, no amendments to be introduced to the Product Information, and thus no regulatory consequences, have been identified by the MAH.

For assessment of the clinical study report → see section 2.3.

6. Rapporteur's overall conclusion on the responses and recommendation

In summary, data obtained in Chinese paediatric PTPs in GENA-40 do not change the favourable benefit risk profile of *Human-cl rhFVIII* in children. The presented data do not warrant any update of the Product information and no regulatory actions are expected to be required. However, prior to a final recommendation, additional clarifications should be provided by the MAH (see section 7 below).

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

7. Second additional clarification requested

1. The Clinical Expert Overview neglects data obtained in the group of adolescents included in GENA-40 (N=15). However, according to the Paediatric Regulation (No 1901/2006) and e.g. ICH E11, the group of adolescents (i.e. patients aged 12 to 18 years) represents a subset of the paediatric population.

   Hence, as part of this Article 46 procedure, the MAH should provide a critical discussion of results obtained in adolescents (including PK data) and confirm the statement that the new paediatric data obtained in GENA-40 (i.e. from children <12 years and adolescents) does not warrant any amendments to be introduced to the PI and that no regulatory consequences were identified.

2. For the group of 6 - <12 year old children included in GENA-40, Table 3 of the Clinical Expert Overview specifies a range of 1-56 infusions and total doses ranging from 29.4 to 2054.9 IU/kg (mean: 156.1 IU/kg) to treat bleeding episodes. Similarly, the synopsis and section 11.4.7 (Efficacy conclusions) of the CSR state that (across all age groups) "*The median number of infusions per BE was 1.0 (IQR: 1.00, 2.00; range: 0-56), and the median dose per episode/kg body weight was 37.97 IU/kg (IQR: 34.15, 72.30; range: 0-2055)*. However, according to Table 19 of the CSR, BEs in GENA-40 were treated with up to 110 infusions and Table 14.2.2.3-1 of the CSR further specifies a median dose per BE/kg body weight of 35.71 IU/kg (mean: 118.57 IU/kg; range: 26.69-4036.6) in the group of 6 - <12 year old children. Furthermore, Listing 16.2.4-1 specifies that indeed the 11-year old patient (included in the PP population) received 110 infusions (over a period of 59 days) with a total dose of 4036.6 IU/kg for the treatment of a spontaneous joint bleed.

   Hence, the MAH is requested to provide clarification on these contradicting statements and ensure consistency across and within both documents (i.e. CSR and Clinical Expert Overview).

8. MAH responses to 2nd clarification request and assessment of the responses

Question 1

The Clinical Expert Overview neglects data obtained in the group of adolescents included in GENA-40 (N=15). However, according to the Paediatric Regulation (No 1901/2006) and e.g. ICH E11, the group of adolescents (i.e. patients aged 12 to 18 years) represents a subset of the paediatric population.

Hence, as part of this Article 46 procedure, the MAH should provide a critical discussion of results obtained in adolescents (including PK data) and confirm the statement that the new paediatric data obtained in GENA-40 (i.e. from children <12 years and adolescents) does not warrant any amendments to be introduced to the PI and that no regulatory consequences were identified.

MAH's response

The data of the adolescent patient population was added to the Clinical Expert Overview. A revised version of the Clinical Expert Overview has been attached to section 2.5 of the eCTD.

Assessment of the MAH's response

As requested, the MAH included a discussion of data (PK, efficacy and safety) obtained in the 15 adolescent patients included in GENA-40 in the Clinical Expert Overview. In the updated Clinical Expert Overview, the MAH further confirms that these data do not change the overall conclusion that *"no changes to the current Nuwiq SmPC, or the RMP, are required based on the results of the GENA-05 and GENA-40 studies"*. Notably, this position complies with the Rapporteur's previous recommendation which already took the assessment of these data into account (see Sections 2 and 6 above).

Issue **resolved**

Question 2

For the group of 6 - <12 year old children included in GENA-40, Table 3 of the Clinical Expert Overview specifies a range of 1-56 infusions and total doses ranging from 29.4 to 2054.9 IU/kg (mean: 156.1 IU/kg) to treat bleeding episodes. Similarly, the synopsis and section 11.4.7 (Efficacy conclusions) of the CSR state that (across all age groups) *"The median number of infusions per BE was 1.0 (IQR: 1.00, 2.00; range: 0-56), and the median dose per episode/kg body weight was 37.97 IU/kg (IQR: 34.15, 72.30; range: 0-2055)*. However, according to Table 19 of the CSR, BEs in GENA-40 were treated with up to 110 infusions and Table 14.2.2.3-1 of the CSR further specifies a median dose per BE/kg body weight of 35.71 IU/kg (mean: 118.57 IU/kg; range: 26.69-4036.6) in the group of 6 - <12 year old children. Furthermore, Listing 16.2.4-1 specifies that indeed the 11-year old patient (included in the PP population) received 110 infusions (over a period of 59 days) with a total dose of 4036.6 IU/kg for the treatment of a spontaneous joint bleed.

Hence, the MAH is requested to provide clarification on these contradicting statements and ensure consistency across and within both documents (i.e. CSR and Clinical Expert Overview).

MAH's response

The data presented in the statement

"The median number of infusions per BE was 1.0 (IQR: 1.00, 2.00; range: 0-56), and the median dose per episode/kg body weight was 37.97 IU/kg (IQR: 34.15, 72.30; range: 0-2055)"

derived from calculations in Section 14, Table 14.2.2.2-1. The calculation is based on the average on a subject basis, which means that indeed the subject had 110 infusions for 1 BE and no infusions for a second BE. This results in an average of 56 infusions per BE.

However, the MA holder acknowledges that this information should be revised in the context it is given, and instead of reporting the median number of infusions and dosage on a subject basis the data should be reported on a bleeding episode basis. Section 14, Table 14.2.2.2-5 presents the calculation based on bleeding episodes. The Critical Expert Overview as well as the CSR were updated accordingly (revised Critical Expert Overview, Dec 2020 and GENA-40 CSR, Version 2.0, dated 02 Dec 2020). During the preparation of the BLA submission in China, 2 additional errors were noted and corrected in GENA-40 CSR Version 2.0. These 2 corrections do not have any impact on the data provided in the Critical Expert Overview nor on the interpretation of the study results.

During the preparation of the BLA submission in China, 2 additional errors were noted and corrected in GENA-40 CSR Version 2.0. These 2 corrections do not have any impact on the data provided in the Critical Expert Overview nor on the interpretation of the study results. The 2 additional corrections are as follows:

1. Correction of translation of an SAE report text (GENA-40 CSR, Section 12.3.2, page 71)
2. Correction of IVR calculations (GENA-40 CSR, Section 11.4.1.3.2; Table 26, Table 27 and Table 28)

A minor programming error regarding the recovery based on actual potency and standardized to 50 IU/kg was detected which affects Section 16, List 16.2.6.2–1 and 16.2.6.2–3 and Section 14, Table 14.2.4.1-1 to Table 14.2.4.1-24, including corresponding figures.

In GENA-40 CSR Version 2, Table 26, 27, and 28 were revised, as well as the corresponding listings and tables in sections 16 and 14. The difference in the recovery calculation is as follows:

		Recovery (kg/dL)	
Subject ID	Visit	Actual Potency standardized to 50 IU/kg List 16.2.6.2-3 In-Vivo Recovery (IVR) at visits 2020_06_02	Actual Potency standardized to 50 IU/kg List 16.2.6.2-3 In-Vivo Recovery (IVR) at visits 2020_12_01 (corrected)
	3 Months	2.73	2.70
	6 Months / Completion	2.23	2.20
	3 Months	1.43	1.37
	6 Months / Completion	1.51	1.45
	ED 1	2.40	2.47
	ED 1	1.38	1.43
	ED 1	1.33	1.44
	3 Months	1.09	1.37
	6 Months / Completion	1.25	1.57

Assessment of the MAH's response

The MAH clarified that the contradicting statements regarding the average consumption of *Human-cl rhFVIII* for the treatment of BEs originated from calculations on a subject basis rather than on a bleed-

ing episode basis. The MAH's decision to consistently report the consumption data on a bleeding episode basis is acknowledged. The Critical Expert Overview (previous Table 3, Table 4 in the revised document) as well as the CSR (Synopsis, Section 11.4.7 [Efficacy Conclusions], Section 13 [Discussion and overall conclusions]) were updated accordingly. The correction of two additional errors (one of which already previously corrected by an erratum document attached to the CSR) is acknowledged. Both corrections do not affect/change the overall interpretation of study results.

Issue **resolved**

9. Rapporteur's overall conclusion on the 2nd responses and recommendation

In summary, data obtained in Chinese paediatric PTPs in GENA-40 do not change the favourable benefit risk profile of *Human-cl rhFVIII* in children. The MAH provided appropriate response to requests for supplementary information. The presented data do not warrant any update of the Product information and no regulatory actions are expected to be required.

☒ **fulfilled, no further clarification requested.**

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