30 April 2020
EMA/371414/2020
Human Medicines Division

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

Vihuma

simoctocog alfa

Procedure no: EMEA/H/C/004459/P46/010.1

Note

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

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1. Introduction

On 17 June 2019, the MAH submitted a completed paediatric study (GENA-15) for Nuwiq/Vihuma, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. At that time, 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 2019, 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, dated 22 Sep 2019):

1. The final clinical study report should be submitted (announced for October 2019 by the MAH).
2. A critical clinical overview is requested.
3. A Listing of all studies of the clinical development program and a statement if the study GENA-15 is part of this program should be submitted.

In response, the MAH submitted the full study report of GENA-15, together with a short clinical overview, on 25 Oct 2019. In addition, the applicant confirmed that the concerned study (GENA-15) is part of the clinical development program of *Human-cl rhFVIII* and provided the requested line listing of all studies included in this program (see Annex). According to the Cover Letter, no regulatory consequences and no amendments to be introduced to the Product Information were identified by the MAH.

2. Scientific discussion

2.1. Information on the development program

The current submission includes the full final clinical study report of GENA-15 "Extension Study for Patients who Completed GENA-05 (NuProtect) – to Investigate Immunogenicity, Efficacy and Safety of Treatment with *Human-cl rhFVIII*", together with a Critical Expert Overview. GENA-15 was clinically completed in December 2018 and a summary report was already provided to the EMA in June 2019. According to the MAH, GENA-15 serves as supportive study in the clinical development program of *Human-cl rhFVIII*. A line listing of all non-clinical and clinical studies conducted as part of this development program is annexed to this report.

Human-cl rhFVIII (simoctocog alfa), currently marketed as Nuwiq and its duplicate Vihuma is a fourth-generation B-domain-deleted (BDD) recombinant human coagulation factor VIII (rFVIII) without chemical modification or protein fusion expressed in genetically modified HEK293F cells. *Human-cl rhFVIII* was approved in Europe in July 2014 for the treatment and prophylaxis of bleeding in patients with haemophilia A in all age groups. This approval was based on data from the GENA clinical trial program, which evaluated the efficacy and safety of *Human-cl rhFVIII* in adult (GENA-01 and GENA-08) and paediatric (GENA-03 study) PTPs suffering from severe haemophilia A, supported by data from GENA-09, and its extension study GENA-04. At the time of approval, three additional paediatric studies were ongoing:

- GENA-13: A long-term extension of the paediatric GENA-03 study in PTPs;
- GENA-05: A paediatric study in PUPs;

- GENA-15: A long-term extension of the GENA-05 study in PUPs who transitioned to PTPs during the course of GENA-05.

In the meantime, the final study report of GENA-13 was submitted (Dec 2016) and has been reviewed in May 2017 within procedure EMEA/H/C002813/P46/005 and in 2018 as part of a Type II variation (EMEA/H/C/WS1506/G). The PUP study GENA-05 is still ongoing (expected clinical completion during Q1 2020). Data from a planned interim analysis were submitted to the EMA in 2016.

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 the final study report for the paediatric clinical extension study GENA-15.

2.3.2. Clinical study

Clinical study number and title

GENA-15: "Extension Study for Patients who Completed GENA-05 (NuProtect) – to Investigate Immunogenicity, Efficacy and Safety of Treatment with Human-cl rhFVIII"

Description

GENA-15 was a Phase 3b, open-label, uncontrolled, multi-centre study comprising 48 previously treated subjects (PTPs) suffering from severe haemophilia A (FVIII:C <1%). GENA-15 was an extension of GENA-05 (study in PUPs) to further investigate the long-term immunogenicity, tolerability and efficacy of *Human-cl rhFVIII* in patients who transitioned to PTPs (≥100 ED) during the course of GENA-05.

Methods

Objective(s)

The objective of GENA-15 was to collect additional long-term data on the immunogenicity, safety and efficacy (in routine and surgical prophylaxis and on-demand treatment of bleeds) of *Human-cl rhFVIII* in PTPs.

Study design

The present study, GENA-15, was a prospective, open-label, uncontrolled, international, multi-centre Phase 3b study designed to investigate the long-term immunogenicity, tolerability and efficacy of *Human-cl rhFVIII* in patients suffering from severe Haemophilia A (FVIII:C <1%) who were originally enrolled in GENA-05 as previously untreated patients (PUPs). Participation in GENA-15 was offered to all patients who completed GENA-05 in accordance with the study protocol, provided that *Human-cl rhFVIII* was not registered and ready for launch in the respective country at that point in time. Hence, participation in GENA-15 enabled patients who completed GENA-05 to continue treatment with *Human-cl rhFVIII* until commercially available. In GENA-05, PUPs were followed over a period of 100 EDs. Consequently, all patients entering GENA-15 were previously treated patients (PTPs) with a history of at least 100 EDs to *Human-cl rhFVIII*.

During the course of GENA-15, exposure to *Human-cl rhFVIII*, its efficacy in the prevention and treatment of bleeds, the frequency of break-through bleeds (in case of prophylactic treatment), the product's efficacy in surgical prophylaxis, and its overall safety and tolerability were thoroughly assessed. Safety was monitored by recording adverse events (AEs) and measuring laboratory values, vital signs, and physical examination. Furthermore, in the course of the follow-up visits (scheduled to be performed every 6 months after the Screening visit) the product's immunogenicity was assessed by applying a modified Bethesda assay to detect FVIII inhibitors (cut-off ≥ 0.6 BU/mL).

Patients completed the study by switching to marketed Factor VIII concentrate, the latest 2 years after the screening visit. In any event, the general clinical completion date was scheduled as 31-Dec-2018.

Study population /Sample size

A total of 48 PTPs (who completed the PUP study GENA-05) entered GENA-15, received at least one dose of *Human-cl rhFVIII* and were included in the safety database. One patient received only a single dose of *Human-cl rhFVIII* and had no data collected post-treatment. This subject was excluded from the intention-to-treat (ITT) analysis, leaving a total of 47 ITT patients.

Treatments

During the course of GENA-15, prophylactic treatment was recommended, but finally, it was the decision of the responsible treating physician whether patients were treated prophylactically or on-demand.

Prophylactic treatment:

Patients were to be treated prophylactically with a recommended dose of > 20 IU FVIII/kg body weight (BW). The frequency of treatment depended on the patient's clinical situation. 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 50-80 IU FVIII/kg BW to achieve an intended target peak level of 100% to 120%. Repeat dose of >20 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 1 dose every 12-24 hours if needed. Trough levels should be maintained at ≥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 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%.

Outcomes/endpoints

The following outcome parameters were investigated:

- Immunogenicity of *Human-cl rhFVIII*
- Efficacy of prophylactic treatment
- Efficacy of treatment of bleeds
- Efficacy of surgical prophylaxis
- Safety and tolerability

Statistical Methods

In GENA-15, no inferential analysis involving formal hypothesis testing was planned; no formal sample size estimation was performed. Results of the study were presented using descriptive statistics.

Results

Recruitment/ Number analysed

A total of 48 patients who completed GENA-05 were enrolled and treated with *Human-cl rhFVIII* at 15 investigational centres (in Canada, France, Georgia, India, Moldova, Poland, Ukraine, United Kingdom, and United States), and included in the safety analysis population. One patient (#15-96-07) received a single dose of *Human-cl rhFVIII* but had no data collected post-treatment. This patient was excluded from the

intention-to-treat population (ITT population), resulting in a total of 47 patients in the ITT population. All 47 patients of the ITT population received prophylactic treatment and were included in the PROPH population.

Of the 128 bleeding episodes (BEs) reported during the course of GENA-15, 111 were treated with *Human-cl rhFVIII* and constituted the BLEED population. Of a total of 5 surgeries, 4 were treated with *Human-cl rhFVIII* and constituted the SURG population.

A total of 7 patients were excluded from the PP population because of major protocol deviations. These were either the use of prohibited concomitant medication or deviations from the scheduled prophylactic treatment intervals. A total of 4 patients prematurely discontinued the study. Reasons for discontinuation were: Lost to follow up (2 cases), a case of product switch to EHL (#15-87-01), and a case of SAE (neuroblastoma in patient #15-55-19, which prevented the patient from further keeping the study visit schedule according to protocol).

Baseline data

The age of enrolled patients ranged from 1.3 to 11.9 years, with a median of 2.8 years. At the time of enrolment, a total of 41 PTPs were aged 1-5 years and 7 PTPs were aged 6-12 years. The mean ± SD duration of participation in the study (= treatment duration) was 29.4 ± 6.9 months (median: 30.1 months, ranging from 9.6 to 53.2 months). The majority of patients were White (36 patients); 9 were Asian, 1 patient was American Indian or Alaska Native, and 2 patients had "other" documented as race. The majority of patients (33 patients, 71.7%) had *F8* gene mutations classed as being of high risk for inhibitor formation. Sixteen (33.3%) patients had a family history of haemophilia; 3 of these patients (18.8%) had a family history of inhibitors to FVIII.

Efficacy results

Prophylactic treatment:

All patients in GENA-15 received prophylactic treatment with *Human-cl rhFVIII*, with the majority of patients (>70%) on a 2-time per week prophylactic schedule at their 6-, 12-, and 18 month study visits. Overall, few changes in prophylactic schedules occurred, with 98.8% of infusions showing no change in schedule compared to previous infusions. The mean (SD) duration of prophylactic treatment was 20.6 (6.5) months and the average dose per prophylactic injection was 35.3 (14.0) IU/kg BW. Seventeen of the 48 patients in the study (35.4%) had no BEs during the study. Of the 47 patients in the ITT population, 31 (66.0%) experienced BEs of any type and 13 (27.7%) experienced spontaneous BEs.

The overall prophylaxis efficacy assessment at the end of study was 'excellent' (monthly rate of spontaneous BEs <0.75) in all 47 (100.0%) patients in the ITT population. For spontaneous BEs, the calculated mean ABR (based on a negative binomial model) was 0.283 (95% CI: 0.153–0.527). For traumatic BEs, the mean ABR was 1.209 (95% CI: 0.739–1.979) and for all types of BEs, the mean ABR was 1.620 (95% CI: 1.086–2.416).

Treatment of BEs:

During the course of GENA-15, 29 patients experienced a total of 128 BEs. Of these, 111 bleeds were treated with *Human-cl rhFVIII*. These were 15 (13.5%) spontaneous, 89 (80.2%) traumatic, 3 (2.7%) post-operative, and 4 (3.6%) BEs documented as 'other'. 63 (56.8%) BEs were minor and 48 (43.2%) were moderate to major. No major to life-threatening bleeds occurred. BEs were most common in the knee (19

[17.1%]), oral cavity (17 [15.3%]), and leg (13 [11.7%]). 'Other' sites of bleeding were mainly BEs characterised by multiple sites and accounted for a total of 32 (28.8%) events. Efficacy assessment of bleeding episodes was performed at the end of each bleed by the patient's parent(s)/legal guardian(s) (together with the Investigator in case of on-site treatment) based on a 4-point rating scale.

Most BEs (78.4%) were resolved with 1 or 2 infusions of *Human-cl rhFVIII*. The mean (±SD) number of infusions per BE was 1.8 (±1.44, range: 1-8), and the mean dose/kg body weight administered per episode was 36.8 IU/kg (± 13.55, range: 14.4-94). The majority of BEs were rated as having 'excellent' (52.3%) or 'good' (25.2%) treatment efficacy, giving a success rate of 77.5%; treatment efficacy was rated as 'moderate' for 21 (18.9%) BEs (8 of these occurred in Patient #15-55-13) and as 'none' for 3 (2.7%) BEs (all were traumatic BEs in Patient #15-55-13).

Surgical prophylaxis:

During the course of GENA-15, a total of 3 patients underwent 4 surgical procedures. Two of these surgeries were minor and 2 were major. The two major procedures (Laser adenoidectomy in patient #15-62-03 and religious circumcision in patient # 15-95-03) had an overall efficacy assessment performed jointly by the haematologist and surgeon, both rated as having 'excellent' efficacy (with a total dose of 175.6 and 184.9 IU/kg, respectively). The other 2 surgeries (both minor procedures; tooth extractions) could not be assessed as only limited data were available due to both procedures having taken place outside the study site. One further surgery performed during the course of GENA-15 was not treated with *Human-cl rhFVIII* and was therefore not included in the SURG population.

Safety results

The safety population of GENA-15 comprised all 48 patients who received at least one dose of *Human-cl rhFVIII*. Patients had a mean of 179 days of exposure to *Human-cl rhFVIII*, received a mean of 180 infusions and a mean total dose per kg BW of 6,404.5 IU.

A total of 29 (60.4%) patients experienced treatment-emergent adverse events (AEs). These were observed after 122 out of 8,646 total infusions (1.4%) administered during the study. Of the 48 patients in the SAF population, 27 (56.3%) experienced mild, 14 (29.2%) moderate, and 3 (6.3%) severe AEs. Most AEs were reported only once. The most commonly reported AEs were pyrexia and nasopharyngitis (each reported in 10 [20.8%] patients), cough (7 [14.6%]), varicella (5 [10.4%]), and anaemia, bronchitis, ear infection, and pharyngitis (each reported in 4 [8.3%] patients). Twenty patients (41.7%) in the SAF population experienced AEs that were temporally associated (i.e. they occurred within 24 hours of the respective infusion) with a total of 52 infusions. No AEs were assessed as possibly/probably related to *Human-cl rhFVIII* by the Investigators. AEs assessed as possibly/probably related to *Human-cl rhFVIII* by the Sponsor were pyrexia (4 patients) and headache (1 patient). None of these possibly/probably related AEs were severe and all resolved without sequelae.

There were no deaths reported in GENA-15. A total of 8 serious adverse events (SAEs) were documented in 5 (10.4%) patients. These were: Pneumonia and varicella in 1 patient, epistaxis and a case reported as spontaneous nasal haemorrhage in 1 patient (post-adenoidectomy), gastritis and cellulitis in 1 patient, and a case of neuroblastoma and pneumonia (in one patient each). All SAEs were assessed by the Investigators as not related to *Human-cl rhFVIII*. The case of neuroblastoma was the only SAE which led to permanent discontinuation from the study.

None of the 48 patients in the study developed a neutralising FVIII inhibitor to *Human-cl rhFVIII.* No cases of thromboembolism or hypersensitivity were reported.

2.3.3. Discussion on clinical aspects

In accordance with article 46 of regulation (EC) No 1901/2006 for paediatric studies, the MAH submitted the final study report of GENA-15, together with a short Clinical Expert Overview. GENA-15 was conducted as supportive study in the clinical development program of *Human-cl rhFVIII*. Since July 2014, *Human-cl rhFVIII* is authorized in Europe for the treatment and prophylaxis of bleeding in patients with haemophilia A in all age groups. The paediatric approval was primarily based on data obtained in the pivotal study GENA-03, which were subsequently corroborated by the long-term extension study GENA-13. The aim of GENA-15 was to further investigate the long-term immunogenicity, efficacy and safety of *Human-cl rhFVIII* in paediatric PTPs (≥ 100 EDs). Participation in GENA-15 was offered to all patients who completed the PUP study GENA-05, provided that *Human-cl rhFVIII* was not registered and ready for launch in the respective country at that point in time. GENA-15 included a total of 48 previously treated children (41 aged < 6 years, 7 aged 6-12 years; median: 2.8 years, range: 1.3 to 11.9 years) suffering from severe haemophilia A (FVIII:C <1%) and investigated *Human-cl rhFVIII*'s efficacy in routine prophylaxis over an average period of 20.6 months. In addition, GENA-15 adds an evaluation of 111 treated bleeds and 2 surgical procedures to the existing clinical database of *Human-cl rhFVIII*.

Overall, efficacy outcomes obtained in GENA-15 appear largely comparable to previously conducted paediatric trials (GENA-03, GENA-13, and GENA-05) and support the statement of clinical efficacy of *Human-cl rhFVIII* in the treatment of children. A mean total annualized bleeding rate (ABR) of 1.620 (0.283 for spontaneous bleeds) in GENA-15 compares to a value of 2.88 reported in the long-term extension study GENA-13. None of the treated patients had a monthly rate of ≥0.75 spontaneous bleeds. The median number of infusions administered for the treatment of bleeding episodes was 1 in all four studies with broadly comparable proportions of successfully treated events (i.e. 82.4% in GENA-03, 83.0% in GENA-13, 91.7% in GENA-05, and 77.5% in GENA-15). The majority of non-successful treatments in GENA-15 were attributed to a notably poor response of a single subject (14 bleeds in approx. 2 years with 8 efficacy ratings of 'moderate' and 3 of 'none') which turned out to be related to an overall low dosing of *Human-cl rhFVIII* and comparably long dosing intervals exceeding protocol recommendations (i.e. >25 hrs) in the majority of cases. All surgical procedures covered by *Human-cl rhFVIII* in all four studies had an efficacy rating of 'excellent' or 'good', except for one procedure in GENA-05 that had an efficacy rating of 'moderate'.

In GENA-15, the mean dose administered per prophylactic infusion (i.e. 35.3 IU/kg) was consistent with the average doses used in previous trials in PTPs (e.g. 38.9 IU/kg in the pivotal study GENA-03). Notably, compared to previous trials dosing recommendations revealed a substantially greater degree of flexibility in GENA-15 (i.e. >20 IU/kg at a not further specified frequency vs. e.g. 30-40 IU/kg every other day or 3-times weekly in GENA-13). In line with this more liberal approach to dosing, the overall range of individual doses reported in GENA-15 was substantially broader (i.e. 16.6-100.2 IU/kg vs. e.g. 28.5-61.0 IU/kg in GENA-13). Furthermore, compared to previous studies, a substantially lower monthly consumption of *Human-cl rhFVIII* was noted (mean: 329.8 IU/kg in GENA-15 vs. 531.2 IU/kg in GENA-13), consistent with a general trend towards prolonged treatment intervals (i.e. 68.1% of patients at screening and 84.9% at 18-month on a 2x/week regimen).

During the course of GENA-15, *Human-cl rhFVIII* was generally well tolerated. The overall profile of AEs reported in GENA-15 is regarded inconspicuous, consistent with the previously established safety profile of

Human-cl rhFVIII, and does not indicate safety concerns specific to the group of children. Neither review of laboratory results, nor of vital signs or physical findings indicates safety concerns related to the administration of *Human-cl rhFVIII*. None of the 48 patients who participated in GENA-15 developed neutralising antibodies against *Human-cl rhFVIII* and there were no reports of thromboembolism or hypersensitivity.

No AEs were assessed as possibly/probably related to *Human-cl rhFVIII* by the Investigators. The only AEs assessed by the sponsor as possibly/probably related to *Human-cl rhFVIII* were pyrexia (5 events in 4 patients) and headache (1 event in 1 patient). None of these events was severe, and all resolved without sequelae. Both types of AEs are not considered remarkable and are already reflected in section 4.8 of the current SmPC. In light of the additional AE reports from GENA-15, the frequencies of pyrexia (common, ≥1/100 to <1/10) and headache (uncommon, ≥1/1,000 to <1/100) referred to by the current SmPC remain unchanged. Similarly, data from GENA-15 do not change the currently reported frequency of FVIII inhibition in PTPs (uncommon ≥1/1,000 to <1/100). Consequently, it is concurred with the MAH's overall conclusion that the submitted data do not warrant any update of the Product information.

3. CHMP's overall conclusion and recommendation

In summary, at this point in time, data obtained in GENA-15 are not expected to change the favourable benefit risk profile of *Human-cl rhFVIII* in pediatric patients. The presented data do not warrant an update of the Product information and no regulatory actions are expected to be required. However, prior to a final recommendation, additional clarification on some of the reported clinical outcomes (efficacy and safety) should be provided by the MAH.

☒ **Not fulfilled:**

Based on the data submitted, the MAH should provide additional clarifications (see section 4 below).

4. Additional clarification requested / RSI

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

1. Whereas the average dose of *Human-cl rhFVIII* administered per prophylactic injection in GENA-15 was similar to previous trials, the monthly consumption was substantially lower (mean values: 329.8 IU/kg in GENA-15 vs. 527.7 IU/kg in GENA-03 and 531.2 IU/kg in GENA-13). While these differences indicate a general trend towards prolonged dosing intervals, such a trend appears counter-intuitive in light of the comparably huge number of younger children (expected to require rather shorter dosing intervals and higher doses) included in the trial. Hence, the MAH should critically discuss the monthly consumption of *Human-cl rhFVIII* reported in GENA-15 in the context of previous trials (in consideration of the respective age distributions of study participants, the underlying dosing regimens, and the reported efficacy outcomes).
2. The MAH should critically discuss the notably poor efficacy of *Human-cl rhFVIII* in Patient #15-55-13 who, according to listing 16.2.6.2.1-2, experienced a total of 14 bleeds (in approx. 2 years) with 8 efficacy ratings of 'moderate' and 3 of 'none'.
3. While none of the reported AEs were deemed related to *Human-cl rhFVIII* by the investigators, the sponsor assessed a total of 5 events of pyrexia (in 4 patients) and 1 event of headache as possibly/probably related to the IMP. Since no further information on these AEs is given, the MAH should provide additional clarification to justify these differing judgements.
4. The MAH should critically discuss the, compared to previous trials, high frequency of reported cases of potentially drug-related pyrexia and provide additional justification for not considering these as potential manifestations of hypersensitivity.

5. Assessment of the MAH's responses to the RSI

Question 1

Whereas the average dose of *Human-cl rhFVIII* administered per prophylactic injection in GENA-15 was similar to previous trials, the monthly consumption was substantially lower (mean values: 329.8 IU/kg in GENA-15 vs. 527.7 IU/kg in GENA-03 and 531.2 IU/kg in GENA-13). While these differences indicate a general trend towards prolonged dosing intervals, such a trend appears counter-intuitive in light of the comparably huge number of younger children (expected to require rather shorter dosing intervals and higher doses) included in the trial. Hence, the MAH should critically discuss the monthly consumption of *Human-cl rhFVIII* reported in GENA-15 in the context of previous trials (in consideration of the respective age distributions of study participants, the underlying dosing regimens, and the reported efficacy outcomes).

MAH's responses

A summary of parameters relevant to the discussion are presented in the table below.

As GENA-03 and GENA-13 were the first studies performed in young children (initiated in Dec 2010 and Oct 2011, respectively), a conservative approach was taken regarding the recommended prophylactic treatment frequency. In the GENA-03 and GENA-13 studies, only every-other-day or a 3-times-a-week dosage regimen were allowed. By the time of initiation of the GENA-15 study (Mar 2014), data from other studies (namely GENA-03 (final data) and GENA-13 (interim data)) had indicated that *Human-cl rhFVIII* was efficacious and safe when used for prophylactic treatment in younger children. GENA-15 and its parent study GENA-05 (initiated Mar 2013) allowed greater freedom to the Investigators regarding the choice of prophylactic treatment schedule, with the frequency of treatment depending on the patient's clinical situation; the majority of patients in GENA-15 were treated on a 2-time per week schedule at screening (68.1%), 6-months (70.5%), 12-months (79.0%) and 18-months (84.9%). Despite the longer treatment intervals in GENA-15, the Investigators determined that the patients barely required higher doses of *Human-cl rhFVIII* based on their clinical picture. The observed average bleeding rate (ABR) in GENA-15 was low indicating that the chosen prophylactic doses and schedules were appropriate for the patient population in the study.

A comparison of the GENA-15 efficacy results with those of GENA-03 and GENA-13 should be made with caution given the different study populations. A notable decrease in ABR was observed for the younger patient group in the extension study GENA-13 when compared with its parent study GENA-03 (0.336 vs. 1.207), and when comparing GENA-15 with its parent study GENA-05 (0.283 vs. 0.976 [inhibitor-free periods]). This may indicate that lower ABRs were observed in the extension studies as the patients were already used to receive *Human-cl rhFVIII* prophylaxis after having successfully completed the parent studies. Therefore, comparison of the studies should focus on GENA-15 vs. GENA-13.

When comparing the ABR for spontaneous BEs, the mean ABR in GENA-15 (0.283) was comparable to that in the younger patient group (2–5 years) in GENA-13 (0.336), confirming efficacy of Human-cl rhFVIII in younger previously treated patients (mean monthly consumption in the 2–5 years subgroup in GENA-13 was 557.3 IU/kg). As the dosing schedule in GENA-13 did not allow the use of lower frequency dosing as in GENA-15, with a recommended minimum dose in GENA-13 of 30 IU/kg compared to >20 IU/kg in GENA-15, patients would inherently have a higher consumption of *Human-cl rhFVIII* in GENA-13 compared to equivalent patients in GENA-15. In both long-term studies, the majority of patients were indeed well controlled under the respective prophylactic treatments, with 54% of patients (2–5 years) in GENA-13 and 72% of patients in GENA-15 not experiencing any spontaneous bleeding events over the long course of the studies. It is therefore likely that the differences in *Human-cl rhFVIII* consumption are related to the added

flexibility in dosing schedule and dose in GENA-15. Equivalent efficacy was achieved in GENA-15 with a lower *Human-cl rhFVIII* consumption compared to GENA-13; this should be noted as a positive finding for both patients and prescribers. It cannot be ruled out that that inherent undetected differences in the patient populations included in GENA-15 and GENA-13 also had an impact on the consumption of *Human-cl rhFVIII*. A conservative approach when first treating younger patients is still warranted and the instruction in the SmPC that "In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary" is still appropriate.

	GENA-15	GENA-03	GENA-13
Dose recommendation for prophylactic treatment	Patients were to be treated prophylactically with a recommended dose of >20 IU FVIII/kg body weight (BW). The frequency of treatment depended on the patient's clinical situation. In cases of inadequate response, Human-cl rhFVIII administration frequency or dose adjustments could be considered at the Investigator's discretion.	30–40 IU FVIII/kg BW every other day or 3 times weekly until 6 months and ≥50 exposure days (EDs) had been fulfilled. Initially, only every-other-day treatment was allowed as per protocol; the additional option of 3-times-weekly treatment was included by a protocol amendment 6 months after enrolment had started. Two dose escalations of each +5 IU/kg BW were allowed in case of an inadequate response (≥2 spontaneous BEs within one month).	For prophylactic treatment, either a persistent every-other-day or a 3-times-a-week dosage regimen (e.g., Mon-Wed-Fri) was available for selection. Regardless of the prophylaxis interval chosen, the prophylactic dosage regimen was 30–40 IU FVIII/kg BW. Two dose escalations of approximately +5 IU FVIII/kg BW each were recommended if two or more spontaneous BEs within one month were reported. This was monitored by monthly compliance checks.
Age at screening	Mean = 3.5 years	Mean = 6.1 years	Mean = 6.7 years
Number of EDs	Mean =179.4	Mean = 89.8	Mean = 402.1
Duration of prophylactical treatment, months	Mean = 20.6	Mean = 6.6	Mean = 29.2
Average dose of Human-cl rhFVIII per infusion, IU/kg	Mean = 35.3	Mean = 38.9	Mean = 38.6
Average amount of Human-cl rhFVIII per month of study, IU/kg/month	Mean = 329.8	Mean = 527.7	Mean = 531.2
Mean ABR for spontaneous BEs	0.283	Overall = 1.359 2-5 years = 1.207 6-12 years = 1.531	Overall = 0.671 2-5 years = 0.336 6-12 years = 1.050

Assessment of the MAH's responses

The MAH justified the compared to previous trials substantially lower monthly consumption of *Human-cl rhFVIII* reported in GENA-15 by a generally more conservative approach to dosing in earlier trials. Indeed, a comparison of study protocols reveals a notably greater degree of flexibility in GENA-15 (i.e. >20 IU/kg at a not further specified frequency) when compared to the long-term paediatric study GENA-13 (i.e. doses of 30-40 IU/kg every other day or 3-times weekly). Considering these differences and given the largely excellent prophylactic efficacy reported in GENA-15, the lower monthly consumption of *Human-cl rhFVIII* is considered reasonably justified.

Furthermore, it is concurred with the applicant's view that, given the limitations in comparing data derived from different trials and different study populations, a conservative approach when first treating younger patients is still warranted and that the statement *"In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary"* included in the product's SmPC is still appropriate.

Conclusion
Issue resolved

Question 2

The MAH should critically discuss the notably poor efficacy of *Human-cl rhFVIII* in Patient #15-55-13 who, according to listing 16.2.6.2.1-2, experienced a total of 14 bleeds (in approx. 2 years) with 8 efficacy ratings of 'moderate' and 3 of 'none'.

MAH's responses

Patient Description:
This patient was screened into the preceding study GENA-05 on 30Nov2015 aged 0.9 years (DOB Dec2014), with his first exposure to the study medication on the same day. He was continuously treated prophylactically with a dose of approximately 34.5 IU/kg BW twice per week. He reported 6 bleeding episodes within a period of almost one year (completion date 13Oct2016). Four were categorized "moderate to major", whereas 2 were "minor" bleeds. Of these 6 BEs, 4 were spontaneous and 2 were traumatic, with an outcome rated "good" in 3 cases, "moderate" in 2 cases, and "none" in one case. The BEs were treated according to protocol recommendation, with a dose of 34.64 IU/kg BW on average. Five AEs were reported in the course of GENA-05, and all were typical for this age group: rhinitis (1), rhinopharyngitis (2), common cold (1) and cough (1) - none of these classified as product related or SAE.

When joining GENA-15 on 13Oct2016 with 103 EDs, the patient was aged 1.8 years. He continued a twice weekly prophylactic treatment with an average dose of 32.5 IU/kg BW per ED in accordance with the study protocol; in April/May 2017, he switched to three times per week. In the further course, he reported the following 5 AEs: stomatitis (1), chronic pulpitis (1), acute periodontitis (1), pharyngotonsillitis (1), and chronic periodontitis exacerbation (1) – none classified as product related or SAE. FVIII-antibodies were not detected during the course of both studies.

Discussion of Bleedings in GENA-15:
In fact, as can be seen from below (Tables 2 and 3), the patient reported 14 bleeds (5 "minor", and 9 "moderate to major"), with efficacy rating assessed as 'good' in 3 cases, 'moderate' in 8 cases, and 'none' in 3 BEs. It should be noted that only one out of these 14 bleeds was spontaneous, whereas 9 were traumatic, one was post-operative (tooth extraction), and another 3 were categorized as "other" (dentist's treatments).

Overall, the prophylactic treatment with Human-cl rhFVIII worked well in this patient, with just one spontaneous bleeding episode reported during an observational period of more than 1 ½ years. The majority having been traumatic bleeding episodes, or were related to dental procedures. The bleeding events were in general treated with a relatively low dose as can be seen in Table 2. The protocol allowed more flexibility in the treatment of bleeds. As an example, for moderate to major BEs, the recommended dose was 30-40 IU/kg BW to achieve an intended target peak level of about 60% to 80%. Effectively, the average dose administered to this patient was 33.6 IU/kg BW. In the light of the patient's long-lasting bleeding episodes, dose adjustments in the treatment of ongoing BEs would have been required.

When further looking into the intervals of treating BEs, the protocol recommends (in addition to the dose range as outlined above) to repeat the dose every 6 to 24 hours until the BE is resolved. However, it can be seen that in this patient, the repeated dossing within 24 hours for moderate to major bleeds exceeded the recommendations:

BE #	Date	start of actual infusion	end of previous infusion (preceding day)	Time difference
BE 05	01.06.2017	19:40	18:35	**> 25 hrs**
BE 10	02.11.2017	13:40	12:35	**> 25 hrs**
BE 11 | BE 14[1]	12.12.2017	13:10	12:05	**> 25 hrs**
	15.12.2017	12:40	11:30	**> 25 hrs**
	16.12.2017	12:55	12:45	**> 24 hrs**
BE 13	07.10.2018	11:45	11:05	**> 24 hrs**
	08.10.2018	14:20	11:50	**> 26 hrs**

Thus, these long intervals between BE treatments might have had a significant impact considering the relatively long bleeding times and the comparably low efficacy of these treatments in this patient.

In summary, however, it should be reiterated that the protocol provided recommendations only, and all modifications in terms of dose and frequency were at the discretion of the Investigators throughout the study, even though the low dosing in the treatment of BEs as chosen by the Investigator, in addition to the long infusion intervals in the treatment of BEs, can be regarded as untypical in patients with such bleeding profiles.

More details can be found on the next tables:

Table 2: Overall Bleeding Overview for Patient 15-55-13:

BE#	Bleeding Site	Type	Severity	Age at BE (years)	Total dose administered (IU)	Total dose per kg (IU/kg)	Dose per infusion (IU/kg)	Duration (days)	No of infusions	Efficacy
BE01	Arm left	traumatic	minor	2,11	1.500	100,00	50,00	3	2	good
BE02	Other: Coccyx	traumatic	minor	2,33	2.000	131,65	32,91	4	4	none
BE03	Arm left	traumatic	minor	2,41	1.000	63,29	31,65	2	2	good
BE04	Oral cavity	other	mod/major	2,42	1.000	63,29	31,65	2	2	good
BE05	Other: Right Glutea	traumatic	mod/major	2,44	1.500	94,94	31,65	3	3	moderate
BE06	Oral cavity	other	mod/major	2,51	4.000	253,16	31,65	5	8	none
BE07	Other: Chin	traumatic	minor	2,68	2.500	158,23	31,65	3	5	moderate
BE08	Other: Chin	traumatic	mod/major	2,70	3.000	189,87	31,65	4	6	none
BE09	Oral cavity	other	mod/major	2,80	2.000	126,58	31,65	3	4	moderate
BE10	Leg right	traumatic	mod/major	2,87	2.000	126,58	31,65	5	4	moderate
BE11	Knee right	traumatic	mod/major	2,98	3.000	193,55	32,26	6	6	moderate
BE14[1]	Arm right	traumatic	mod/major							moderate
BE12	Oral cavity	post-op	minor	3,75	2.000	133,33	33,33	4	4	moderate
BE13	Other: Sacroiliac joint	spontanous	mod/major	3,79	3.500	233,33	46,67	4	5	moderate

[1] *BE 11 and BE 14 occurred in parallel*

Table 3: Overview on efficacy ratings after treatment of BEs:

Patient ID: 15-55-13			
Efficacy	**total**	**minor**	**moderate/major**
good	**3**	2	1
moderate	**8**	2	6
none	**3**	1	2
BEs total	**14**	**5**	**9**

Assessment of the MAH's responses

The MAH provided additional information on Patient #15-55-13 and the bleeding episodes in question. According to the MAH's response, the poor efficacy ratings reported in this patient correlated with a relatively

low on-demand dosing of *Human-cl rFVIII* (i.e. within the lower range of recommendations as given in the study protocol or the product's SmPC) and comparably long dosing intervals exceeding protocol recommendations (i.e. > 25 hrs) in the majority of cases. Importantly, Patient #15-55-13 was not tested positive for FVIII-antibodies and his overall AE profile remained unremarkable. None of the AEs reported in this subject was classified as product-related or serious in nature. Furthermore, it was noted that during an observational period of more than 1.5 years, only one of the bleedings reported in this patient was spontaneous. Hence, considering the MAH's response, it is agreed that the poor on-demand efficacy ratings reported for Patient #15-55-13 are reasonably explained by an overall low dosing of *Human-cl rFVIII* combined with unusually long infusions intervals.

Conclusion

The MAH provided sound justification for the poor efficacy ratings of Patient #15-55-13.
Issue resolved

Question 3

While none of the reported AEs were deemed related to *Human-cl rhFVIII* by the investigators, the sponsor assessed a total of 5 events of pyrexia (in 4 patients) and 1 event of headache as possibly/probably related to the IMP. Since no further information on these AEs is given, the MAH should provide additional clarification to justify these differing judgements.

MAH's responses

The assessment of possible relatedness for these specific AEs is based on the fact that the AEs occurred with a latency of 0 days to the administration of study drug and no alternative potential cause for the AEs was identified (e.g. no other documented concurring medical condition or AE). As both pyrexia and headache were listed in the summary of safety profile in the Human-cl rhFVIII Investigator's Brochure, the assessment of "possible relatedness" was considered appropriate and in line with the clinical study protocol. A causal relationship between the IMP and an AE carried at least a reasonable possibility given the temporal relationship of event onset and study drug administration, i.e., the relationship could not be ruled out.

Assessment of the MAH's responses

The MAH does not further elaborate on the apparent discrepancies between the investigator's and the sponsor's judgments. However, the MAH points out that the sponsor's assessments were primarily based on the absence of an alternative potential cause and a temporal relationship to the administration of *Human-cl rhFVIII* (i.e. latency of <24 h). This approach is in line with the study protocol. Hence, the sponsor's ratings appear reasonable and no open issues remain with regard to their classification. Notably, both of these AEs (i.e. pyrexia and headache) are already listed in the ADR table in section 4.8 of the product's SmPC.

Conclusion
The MAH provided appropriate justification for the AE ratings in question.
Issue resolved

Question 4

The MAH should critically discuss the, compared to previous trials, high frequency of reported cases of potentially drug-related pyrexia and provide additional justification for not considering these as potential manifestations of hypersensitivity.

MAH's responses

The four assessments of potentially drug-related pyrexia were made strictly on the basis of their latency; there are no further explanations that would help rule out a potential relationship between IMP and AE. However, when comparing the frequency of possibly related pyrexia with that of previous studies, it has to be kept in mind that the GENA-05 study was performed in PUPs, i.e. very young patients; in this population, pyrexia occurs with a higher frequency than in the paediatric population of higher age or in adults with a mature immune system. Consequently, it appears appropriate to not classify the occurrence of pyrexia in this age group as a hypersensitivity AE, but to classify it as a general disorder.

Assessment of the MAH's responses

In essence, the MAH explains the compared to previous trials higher frequency of potentially drug-related pyrexia by the comparably young age of the investigated study population (all pts. were originally enrolled as PUPs in GENA-05). In consideration of the very young age of the majority of study participants (median age: 2.8 years), it is agreed with the MAH that the higher frequency of this AE can be explained by a generally higher likelihood of developing pyrexia at this age. Hence, even though potential manifestations of hypersensitivity cannot be excluded with certainty, the reported cases of potentially drug-related pyrexia do not trigger concerns questioning the overall favourable safety profile of *Human-cl rFVIII* in the paediatric population.

Conclusion
Issue resolved.

6. CHMP's overall conclusion and recommendation

In summary, data obtained in GENA-15 do not change the favourable benefit risk profile of *Human-cl rhFVIII* in pediatric patients. The MAH provided appropriate response to requests for supplementary information. The presented data do not warrant an update of the Product information and no regulatory actions are required.

P46 010

☒ **Fulfilled**

Annex. Line listing of all 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	GENA-11	2010-023242-69	16-Jul-2013	17-Jan-2014

Severe Haemophilia A – Extension Study to GENA-01				
Clinical Study To Investigate the Efficacy, Safety, And Immunogenicity of Human-cl rhFVIII in Previously Treated Patients with Severe Haemophilia A	GENA-08[1]	2009-011055-43	19-Jul-2012	29-May-2013
Prospective Clinical Study in Children with Severe Haemophilia A to Investigate Clinical Efficacy, Immunogenicity, Pharmacokinetics, and Safety of Human-cl rhFVIII	GENA-03[1]	2010-018644-14	15-Feb-2013	29-May-2013
Clinical Study in Previously Treated Children with Severe Haemophilia A to Investigate the Long-Term Immunogenicity, Tolerability and Efficacy of Human-cl rhFVIII	GENA-13	2011-001785-17	22-Nov-2016	07-Dec-2016
Clinical Study to Investigate the Pharmacokinetics, Efficacy, Safety and Immunogenicity of Human-cl rhFVIII in Previously Treated Patients with Severe Haemophilia A	GENA-09[2]	2008-006172-29	14-Dec-2010	29-May-2013
Clinical Study to Investigate the Long-Term Safety and Efficacy of Human-cl rhFVIII in Previously Treated Patients with Severe Haemophilia A	GENA-04[2]	2009-014422-41	22-Mar-2012	29-May-2013
Immunogenicity, Efficacy and Safety of Treatment with Human-cl rhFVIII in Previously Untreated Patients with Severe Haemophilia A	GENA-05[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