27 June 2019
EMA/467702/2019
Human Medicines Evaluation Division

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

ADYNOVI

rurioctocog alfa pegol

Procedure no: EMEA/H/C/004195/P46/008.1

Note

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

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1. Introduction

On the 12th of November 2018, the MAH submitted a completed study for Adynovi (Rurioctocog alfa pegol/B02BD02) which also includes a paediatric subset, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study 261302 "A Phase 3b Continuation Study of the Safety and Efficacy of PEGylated Recombinant Factor VIII (PEG-rFVIII; BAX 855) in Prophylaxis of Bleeding in Previously Treated Patients with Severe Hemophilia A" is part of a clinical development program. As per the "Guideline on clinical investigation of recombinant and human plasma-derived factor VIII products" (EMA/CHMP/BPWP/144533/2009 rev. 1), 200 previously treated patients (PTPs) need to be followed up to a total of 100 exposure days in the context of the clinical development plan for these kind of products within 4 years after obtaining the marketing authorisation as a post-approval measure. This requirement was also reflected in the PIP.

2.2. Information on the pharmaceutical formulation used in the study

BAX 855 (rurioctocog alfa pegol) is a novel longer-acting full-length recombinant factor VIII (rFVIII) modified with polyethylene glycol ([PEG]ylated). The rFVIII molecule is identical to the full-length albumin/plasma free manufactured octocog alfa known as ADVATE. Controlled PEGylation yields a product with a 1.3 to 1.5-fold extended half-life (T1/2) compared with the ADVATE parent molecule.

The BAX 855 manufacturing process provides for high margins of safety with respect to adventitious viruses by (i) the use of recombinant CHO cell lines which have been subjected to a series of rigorous virus detection assays over many years; (ii) no addition of any materials of animal or human origin during production, thus minimizing the risk of inadvertent introduction of adventitious viruses into the process; (iii) the contribution of the purification scheme for ADVATE, which is the starting material for BAX 855, to the viral safety of the product; and (iv) the integration of an effective virus inactivation step into the manufacturing process, i.e., solvent/detergent (S/D) treatment.

BAX 855 as used in Study 261302 is formulated as a sterile, highly purified protein preparation in lyophilized form for intravenous (i.v.) infusion. It is provided in single dose vials along with a vial of diluent (2 or 5 mL Sterile Water for Injections, as available). No pediatric formulation is provided. A minimum of 4 lots of BAX 855 of 4 nominal potencies were to be used in the study, depending upon availability: 250, 500, 1,000 and 2,000 International Units (IU)/vial.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

• Study number 261302: *"A Phase 3b Continuation Study of the Safety and Efficacy of PEGylated Recombinant Factor VIII (PEG-rFVIII; BAX 855) in Prophylaxis of Bleeding in Previously Treated Patients with Severe Hemophilia A"*

2.3.2. Clinical study

The MAH submitted a final report for Study 261302:

"A Phase 3b Continuation Study of the Safety and Efficacy of PEGylated Recombinant Factor VIII (PEG-rFVIII; BAX 855) in Prophylaxis of Bleeding in Previously Treated Patients with Severe Hemophilia A"

Study Period:
Date of First Treatment: 15 October 2013
End of Study Date: 02 March 2018

Description

This was a Phase 3b, prospective, open label, multi-center study to evaluate the safety and efficacy of BAX 855 for prophylactic use and the control of bleeding episodes in approximately 200 pediatric and adult PTPs ≤75 years of age with severe hemophilia A. The study was to include subjects from other BAX 855 studies to receive either a fixed or a pharmacokinetically-tailored (PK-tailored) prophylactic BAX 855 dose regimen for at least 100 exposure days (EDs), as accumulated across all BAX 855 studies. BAX 855-naïve subjects could also be included after enrollment in the pivotal and pediatric BAX 855 studies had been closed.

Methods

Objectives

Co-primary objectives:

–   To determine the safety of BAX 855 based on the incidence of FVIII inhibitory antibody development

–   To determine the efficacy of BAX 855 based on the annualized bleed rate (ABR) of spontaneous bleeding episodes

Secondary objectives:

Efficacy:

–   To determine the total ABR (spontaneous and traumatic bleeding episodes)

–   To determine the overall hemostatic efficacy rating of BAX 855 for treatment of breakthrough bleeding episodes

–   To determine the length of intervals between bleeding episodes

–   To characterize the hemostatic efficacy of BAX 855 for treatment of bleeding episodes by the number of BAX 855 infusions for treatment

–   To determine total weight-adjusted consumption of BAX 855 for prophylaxis and for treatment of bleeding episodes

–   To assess Patient Reported Outcomes (PROs) over time for subjects receiving BAX 855

Safety:

    – To determine the safety of BAX 855, as assessed by the occurrence of adverse events (AEs) and changes in vital signs and clinical laboratory parameters

    – To determine the immunogenicity of BAX 855

Tertiary/exploratory objectives:

    – To assess patient satisfaction, patient activity levels, and health resource use over time for subjects receiving BAX 855

    – To determine the potential correlation between TGA parameters, FVIII trough levels and ABR

Study design

This was a Phase 3b, prospective, open label, multi-center study to evaluate the safety and efficacy of BAX 855 for prophylactic use and the control of bleeding episodes in approximately 200 pediatric and adult PTPs ≤75 years of age with severe hemophilia A. The study was to include subjects from other BAX 855 studies and BAX 855-naïve subjects.

Subjects were to receive either a fixed-dose regimen with BAX 855 consisting of 45 ± 5 International Units (IU)/kg per prophylactic infusion for subjects aged ≥12 years or 50 ± 10 IU/kg per prophylactic infusion for subjects aged <12 years twice weekly or, subjects could decide to receive a pharmacokinetically tailored (PK-tailored) prophylactic BAX 855 dose regimen based on the subject's individual PK to maintain FVIII trough levels of ≥3%. The frequency of PK-tailored prophylactic BAX 855 dosing was to be at least twice weekly. Subjects were to participate in the study until they had reached at least 100 exposure days (EDs) (as accumulated across all BAX 855 studies).

Study population /Sample size

To be eligible to participate in this study, candidates were required to meet the following eligibility criteria at the time of signing the informed consent or at the EOT Visit of the previous study. Potential subjects from other BAX 855 studies including the Phase 2/3 pivotal, surgery, pediatric PTP, or other BAX 855 studies, will be qualified for the continuation study based on meeting the inclusion criteria and completion of that study's End of Study Visit assessments.

Main Inclusion Criteria:

Subjects Transitioning from other BAX 855 Studies:

- Subject has completed a previous BAX 855 study and is willing to immediately transition into this continuation study
- Subject is ≤ 75 years of age at screening of the previous BAX 855 study
- Subject continues to have a Karnofsky (for subjects aged ≥ 16 years) or Lansky (for subjects aged < 16 years) performance score of ≥ 60

BAX 855-naïve Subjects:

- Subject is ≤75 years of age at screening
- Subject is naïve to BAX 855
- Subject has severe hemophilia A (FVIII clotting activity < 1%) as confirmed by central laboratory at screening after at least a 72-hour washout period

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- Subject aged ≥6 years has documented previous treatment with plasma-derived FVIII concentrates or rFVIII for ≥150 EDs
- Subject aged <6 years has documented previous treatment with plasma-derived FVIII concentrates or rFVIII for ≥50 EDs
- Subject is currently receiving prophylaxis or on-demand therapy with FVIII
- Subject has a Karnofsky (for subjects aged ≥ 16 years) or Lansky (for subjects aged < 16 years) performance score of ≥60

<u>Main Exclusion Criteria:</u>

Subjects Transitioning from other BAX 855 Studies:

- Subject had detectable FVIII inhibitory antibodies (≥ 0.6 BU using the Nijmegen modification of the Bethesda assay) as confirmed by central laboratory at screening
- Subject has developed FVIII inhibitory antibodies (≥ 0.6 BU using the Nijmegen modification of the Bethesda assay as determined at central laboratory in a previous BAX 855 study)
- Subject has acquired a hemostatic defect other than hemophilia A (eg, qualitative platelet defect or von Willebrand's disease) in a previous BAX 855 study
- Subject has severe chronic hepatic dysfunction (eg, ≥ 5 times upper limit of normal alanine aminotransferase [ALT], as confirmed by central laboratory at screening)
- Subject has severe renal impairment (serum creatinine > 2.0 mg/dL), as confirmed by central laboratory at screening
- Subject experienced a life-threatening or gastrointestinal bleeding episode within 3 months prior to study entry.
- Subject is scheduled to use other PEGylated drugs during study participation.

BAX 855-naïve Subjects

- Subject has detectable FVIII inhibitory antibodies (≥ 0.6 BU using the Nijmegen modification of the Bethesda assay) as confirmed by central laboratory at screening
- Subject has history of FVIII inhibitory antibodies (≥ 0.6 BU using the Nijmegen modification of the Bethesda assay or the Bethesda assay) at any time prior to screening
- Subject has been diagnosed with an inherited or acquired hemostatic defect other than hemophilia A (eg, qualitative platelet defect or von Willebrand's disease)
- Subject has known hypersensitivity towards mouse or hamster proteins, PEG, or Tween 80
- Subject has severe chronic hepatic dysfunction (eg, ≥ 5 times upper limit of normal ALT, as confirmed by central laboratory at screening)
- Subject has severe renal impairment (serum creatinine > 2.0 mg/dL), as confirmed by central laboratory at screening
- Subject experienced a life-threatening or gastrointestinal bleeding episode within 3 months prior to study entry
- Subject has current or recent (< 30 days) use of other PEGylated drugs prior to study participation or scheduled use of such drugs during study participation

In total, approximately 250 subjects were to be enrolled in this study. This **sample size** was not based on any power calculation for statistical inferences, but on the sample size of previous BAX 855 studies to have 200 evaluable subjects with a minimum of 100 EDs to BAX 855 in accordance with the guidance EMA/CHMP/BPWP/144533/2009.

Treatments

Subjects can enter the Phase 3b continuation study, either directly via BAX 855 Ph 2/3 pivotal, surgery, pediatric PTP, other BAX 855 studies, or as BAX 855 naïve subjects. Dose assignment when entering this study will be based on the subject's participation in previous BAX 855 studies, as follows:

A. On-demand subjects from the Ph2/3 pivotal study with an ABR>0, BAX 855- naïve subjects and subjects joining from the surgery study will receive a fixed dose of BAX 855 45± 5 IU/kg, twice weekly.

B. Subjects from the Ph 2/3 pivotal study (excl. on-demand subjects), the pediatric PTP study, or from other BAX 855 studies, with an ABR>0 will be treated with BAX 855 45-80 ± 5 IU/kg twice weekly.

C. Subjects from the Ph 2/3 pivotal study (incl. on-demand subjects), the pediatric PTP study, or from other BAX 855 studies, with an ABR=0, will be offered BAX855 30-80 IU/kg q5d.

After each consecutive 6 months of being treated in this study, the dose and/or frequency may be adjusted as follows, depending on the subjects spontaneous ABR estimated at those intervals:

A. Subjects achieving an ABR>0 on a twice weekly dosing schedule will continue on BAX855 45-80 ± 5 IU/kg twice weekly.

B. Subjects achieving an ABR=0 on a twice weekly dosing schedule will be offered BAX855 30-80 IU/kg q5d.

C. Subjects achieving an ABR=0 on a q5d dosing schedule will be offered BAX855 30-80 IU/kg q7d.

D. Subjects achieving an ABR≤2 on a q5d or a q7d dosing schedule will be offered to stay on their current dosing schedule

E. Subjects achieving an 2<ABR≤4 on a q7d dosing schedule will be offered to switch back to BAX855 30-80 IU/kg q5d.

F. Subjects achieving an ABR>2 on q5d or ABR>4 on q7d will be switched back to BAX 855 45-80 ± 5 IU/kg twice weekly.

BAX 855 dosages <45 IU/kg can only be offered to subjects with a known PK profile of BAX 855 (from BAX 855 Ph2/3 or BAX 855 PK guided maximum efficacy or BAX 855 surgery).

Furthermore, BAX 855 dosages < 45 ± 5 IU/kg are not permitted in subjects entering the study with ABR>0, however if subjects enter the study with an ABR=0 or develop an ABR=0 within 6 month treatment with BAX855 twice weekly, dosages <45 ± 5 IU/kg are allowable.

For subjects receiving twice weekly prophylaxis and with ABR>2, dosing of BAX 855 may for a 6 month time period target a FVIII trough level of up to a maximum of 10% at investigators discretion and approval by the study medical director.

Subjects meeting either of the following criteria during prophylaxis may have their BAX 855 dose increased and/or frequency of administration increased:

- Two or more spontaneous (not related to trauma) bleeding episodes in the same target joint within any 2-month period, or

- One or more spontaneous (not related to trauma) bleeding episodes in a nontarget joint within any 2-month period

- FVIII trough level < 1% and investigator's estimate that study subject has an increased risk of bleeding

Dose adjustment may take place as follows and only after consultation with the study Medical Director and written documentation of the decision which will be recorded in the eCRF:

- The BAX 855 dose regimen may be increased gradually up to a maximum of 80 ± 5 IU/kg and/or the frequency can be changed to twice weekly.

Treatment of Bleeding Episodes

According to the guidelines outlined in Table 2, BAX 855 (10-60 ± 5 IU/kg) will be used for treatment of bleeding episodes (ie, breakthrough bleeding episodes during prophylaxis). These guidelines may be adjusted by the investigator based upon his or her clinical judgment, and if needed, to allow for dosing below 10 ± 5 IU/kg or above 60 ± 5 IU/kg, based on the severity of the bleed. The subject or their caregiver, will rate the severity of the bleeding episode as mild, moderate or severe and will rate his overall response for each bleeding episode 24 h (± 2 h) after initiating treatment. A 4- point Efficacy Rating Scale for Treatment of Bleeding Episodes (Table 3) will be used to assess efficacy of BAX 855. Efficacy will not be assessed if ADVATE or any other FVIII product is administered for treatment of bleeding episodes. Efficacy will be defined as a response of good or excellent. As per Table 3, multiple infusions of BAX 855 may be administered for the treatment of a bleeding episode. The overall response to all infusions combined is the rating that will be recorded.

When the treatment is controlled, it allows the administration of BAX 855 infusions to maintain hemostasis (FVIII trough levels of 1%) for a maximum of 24 hours after the bleed resolution if required, or the subject can re-start prophylaxis at the previous BAX 855 dose and schedule. Infusions to maintain hemostasis will count as EDs.

Outcomes/endpoints

Primary Outcome Measures

- Development of inhibitory antibodies to FVIII ($\geq$0.6 BU measured by the Nijmegen modification of the Bethesda assay)
- Spontaneous ABR

Secondary Outcome measures

Efficacy:

- Total ABR (spontaneous and traumatic bleeding episodes)
- Overall hemostatic efficacy rating of BAX 855 for treatment of breakthrough bleeding episodes
- Number of BAX 855 infusions to treat bleeding episodes
- Time intervals between bleeding episodes
- Weight-adjusted consumption of BAX 855

Secondary Safety / Immunogenicity Outcomes:

- Occurrence of AEs and serious adverse events (SAEs)

- Changes in vital signs and clinical laboratory parameters (hematology, clinical chemistry, and lipids)

- Immunogenicity (a 72-hour washout period is required)

  - Binding antibodies (immunoglobulin G [IgG] and immunoglobulin M [IgM]) to FVIII, PEGFVIII, and polyethylene glycol (PEG)

  - Anti-Chinese hamster ovary (CHO) antibodies

<u>Patient-reported outcomes:</u>

Changes from baseline in parent study, if applicable, in the following:

- Bleed and pain severity as measured using the Haemo-SYM questionnaire

- Health-related quality of life (HRQoL) as assessed using the Short Form 36 (SF-36)/ Pediatric Quality of Life Inventory (PedsQL) questionnaires

Exploratory Outcomes Measure

- Patient satisfaction with treatment will be assessed using the Satisfaction Question Set

- Patient Activity Level

- Health resource use data (eg, physician office visits, hospitalizations, length of stay, days missed from work/school)

Statistical Methods

<u>Primary Analysis</u>

The number and proportion (Clopper-Pearson exact 95% CI) of subjects who develop inhibitory antibodies to FVIII will be provided. Only the inhibitory antibodies developed after the first exposure to BAX 855 will be included in the analysis.

The primary outcome measure, the spontaneous ABR, will be assumed to have a negative binomial distribution, and the mean ABR (95% CI) will be estimated using a general estimating equation (GEE) model framework (with a logarithmic link function which is the default for the negative binomial distribution) with treatment regimen as a fixed effect, subject effect as a random effect, age at aseline as a continuous covariate, and the logarithm of follow-up time (in years) as an offset.

<u>Secondary Analyses</u>

- The total ABR (spontaneous and traumatic bleedings) will be estimated and similarly described as the primary efficacy outcome.

- Rate of Success of BAX 855 for treatment of breakthrough bleeding episodes

Success will be defined as a rating of excellent or good using the efficacy rating scale for treatment of bleeding episodes, 24 hours after initiation of BAX 855 treatment for the bleeding episode.

Success proportion (95% CI) will be estimated within a general estimating equation (GEE) model framework. The model will account for the fixed effects of bleeding severity, and the random subject effect.

For the dependent variable (success: yes/no) a binomial distribution and a log link will be assumed, and for the subject effect (defined by a repeated statement) an independence correlation structure will be used to start the estimation. Estimated model parameter values and CI limits will then be back-transformed to the original scale by exponentiation.

- Number of BAX 855 Infusions Needed for the Treatment of Bleeding Episodes: Frequency tables will be prepared for the number of infusions required for the treatment of a bleed. The median number of infusions (and nonparametric 95% CI) will be estimated.

- Time Intervals Between Bleeding Episodes: The average time interval between 2 consecutive bleeding episodes will be computed for each subject. If a subject does not have any bleeding episode then the observation will be censored at the end of the follow-up time of the respective subject. The median (95% CI) of those average time intervals between 2 bleeding episodes will be estimated.

- Weight-Adjusted Consumption of BAX 855: Consumption of BAX 855 will be summarized as average number of BAX 855 infusions and average weight-adjusted consumption of BAX 855 per month.

- Haemo-SYM: Higher scores on the Haemo-SYM indicate worse symptom severity. Changes from Baseline to End of Treatment in the Haemo-SYM scores will be tested for statistical significance, using a Wilcoxon test for paired samples. Improvement in the Haemo-SYM pain subscale of at least 11 points decreasing will be considered a meaningful improvement (a 1 point change on each pain question). Number and proportion of subjects with meaningful improvement in the Haemo-SYM pain subscale will be tabulated.

- SF-36: Lower scores on SF-36 indicate worse HRQoL. Changes from Baseline to End of Treatment in the SF-36 scores will be tested for statistical significance using a Wilcoxon test for paired samples. Improvement in the SF-36 scale of at least 3 points increasing will be considered a meaningful improvement. The number and proportion of subjects with meaningful improvement in SF-36 will be tabulated.

Safety Analysis

Frequency counts and percentages will be calculated for SAEs, occurrence of inhibitory and binding antibodies, occurrence of severe allergic reactions, and occurrence of thrombotic events.

AEs that occurred during or after treatment will be presented in summary tables. AEs will be cross-tabulated for relatedness, seriousness, and severity. AEs will be categorized according to the MedDRA dictionary and summarized by system organ class and preferred term.

Interim Safety Reviews

The first interim safety review will be done when 35 subjects complete 6 months of BAX 855 treatment with 30 to 80 IU/kg q5d.

Descriptive statistics of ABR of this period will be provided, in addition, the number and percentage (95% CI) of subjects with ABR = 0 in this 6-month observation period will be provided.

The second interim safety review will be done when 20 subjects complete 6 months of BAX 855 treatment with 30 to 80 IU/kg q7d.

The analysis of this interim will be the same as the first interim safety review.

An additional safety review is planned upon completion of the phase 2/3 pivotal study.

Results

Recruitment/ Number analysed

A total of 218 subjects were enrolled in the study. **216** subjects received at least 1 infusion of BAX 855 and qualified for the safety (**SAS**) and full analysis (**FAS**) sets. **186 subjects** qualified for the **per-protocol analysis** (PPAS) set of all subjects in the SAS who had no major deviations from the protocol affecting the study results. **30** subjects qualified for the pharmacokinetic analysis set (**PKAS**) of all subjects in the SAS with at least one PK assessment performed in the current study.

Table 5
Analysis Sets by Age Group (EU Categories)
(Study 261302: All Subjects Enrolled Set)

Analysis Set	Age <6 (N=32) n (%)	Age ≥6 to <12 (N=35) n (%)	Age ≥12 to <18 (N=30) n (%)	Age ≥18 (N=121) n (%)	Total (N=218) n (%)
All subjects enrolled set	32 (100.0)	35 (100.0)	30 (100.0)	121 (100.0)	218 (100.0)
Safety analysis set	32 (100.0)	33 (94.3)	30 (100.0)	121 (100.0)	216 (99.1)
Full analysis set	32 (100.0)	33 (94.3)	30 (100.0)	121 (100.0)	216 (99.1)
Per protocol analysis set	23 (71.9)	30 (85.7)	28 (93.3)	105 (86.8)	186 (85.3)
Pharmacokinetic analysis set	6 (18.8)	8 (22.9)	5 (16.7)	11 (9.1)	30 (13.8)

n = Number of subjects in each category. N = Total number of subjects in the relevant analysis set and age group. % = Percentage of subjects in each category relative to the number of subjects in the all subjects enrolled set and age group.

Baseline data

For the 216 subjects treated in the study (SAS), age at informed consent ranged from 1 to 61 years; the mean (standard deviation [SD]) age was 22.8 (15.67) years. Using EU age categories, 32 were <6 years of age, 33 were ≥6 to <12, 30 were ≥12 to <18, and 121 were ≥18 years of age. The subjects had a mean (SD) of 57.0 (39.62) previous EDs to BAX 855 (range: 0 to 277 days).

All but one subject who received BAX 855 in the study were male (215/216; 99.5%). The only female subject (0.5%) was in the ≥6 to <12 years age category.

The majority of subjects were White (152/216; 70.4%), followed by Asian (58/216; 26.9%), and Black or African American (4/216; 1.9%). Ten (10/216; 4.6%) were of Hispanic or Latino ethnicity.

Ten subjects (10/216; 4.6%), all aged <12 years, were naïve to BAX 855; 206 (206/216; 95.4%) had participated in one or more previous BAX 855 studies.

A total of 110 subjects (110/216; 50.9%) had target joints at screening, 106 (106/216; 49.1%) had none. The proportion of subjects with target joints and the number of target joints increased with age. In the <6 years age category, 2/32 subjects (6.3%) had 1 target joint at screening and none had more than 1. In the ≥18 years age category, 87/121 subjects (71.9%) had at least 1 target joint and 22/121 (18.2%) had ≥4 target joints.

Of 216 subjects, 93 (43.1%) had hemophilic arthropathy. Again the proportion of subjects with hemophilic arthropathy increased with age, amounting to 69.4% (84/121 subjects) in the ≥18 years age category.

A total of 25/216 subjects (11.6%), among them 22 adults, had been on an on-demand regimen prior to the study, while the majority of subjects (191/216; 88.4%) had been on FVIII prophylaxis.

Efficacy results

The study evaluated the efficacy of BAX 855 in the treatment of bleeding.

Primary efficacy outcome measure

Spontaneous Annualized Bleed Rate (ABR)

The spontaneous ABR using a generalized linear model was determined for fixed-dose prophylaxis administered twice weekly, every 5 days (q5d), every 7 days (q7d), and for PK-tailored prophylaxis. A subject had to have ≥100 EDs to be included in the analysis.

While on fixed-dose, twice-weekly prophylaxis, a total of 186 subjects had 372 spontaneous bleeds. Using the generalized linear model, the point estimate (95% CI) for the spontaneous ABR was 1.197 (0.918 - 1.561). It was similar (1.259 [0.876 - 1.812]) for subjects ≥18 years of age, lower for subjects aged <6 years (0.656 [0.394 - 1.094]) and for subjects ≥6 to <12 years (0.762 [0.438 - 1.325]), and higher for the ≥12 to <18 year age category (1.768 [1.093 - 2.859]). The point estimate (95% CI) for the total ABR in this prophylactic regimen was 2.230 (1.852 - 2.686). ABRs during long-term administration of BAX 855 using a twice-weekly prophylactic regimen were comparable to outcomes over ≥50 EDs in the pivotal and pediatric studies. In these studies, subjects ≥12 years on twice-weekly prophylaxis (N = 101) had a mean (SD) spontaneous ABR of 2.1 (3.5) and a mean (SD) overall ABR of 3.7 (4.7), and in subjects <12 years (N = 66) the point estimate (95% CI) for the mean was 1.16 (0.74 - 1.83) for the spontaneous ABR and 3.04 (2.21 - 4.19) for the overall ABR.

Subjects who qualified for fixed-dose prophylaxis q5d (56 subjects) had a total of 115 spontaneous bleeds while on this regimen. The point estimate (95% CI) for the spontaneous ABR on this regimen was 1.323 (0.873 - 2.006). It was similar for subjects ≥12 to <18 years and ≥18 years. No subjects <12 years were on this regimen. The point estimate (95% CI) for the total ABR for this prophylactic regimen was 2.095 (1.537 - 2.855).

Subjects who qualified for fixed-dose prophylaxis q7d (15 subjects) had a total of 23 spontaneous bleeds while on this regimen. The point estimate (95% CI) for the spontaneous ABR on this regimen was 1.775 (0.776 - 4.056). For the 2 subjects aged ≥12 to <18 years who qualified for this regimen, it was 0.000 (0.000 - 0.000). For subjects ≥18 years, the point estimate (95% CI) for the spontaneous ABR was 2.215 (0.914 - 5.368). No subjects <12 years were on this regimen. The point estimate (95% CI) for the total ABR in this prophylactic regimen was 2.735 (1.437 - 5.204).

While on a PK-tailored regimen, 25 subjects included in the analysis had 35 spontaneous bleeds. The point estimate (95% CI) for the spontaneous ABR was 0.964 (0.542 - 1.714). It was comparable among all EU age categories ranging from 0.842 (0.122 - 5.821) in subjects aged ≥12 to <18 years to 1.006 (0.449 - 2.252) in subjects ≥18 years. The point estimate (95% CI) for the total ABR in this prophylactic regimen was 2.638 (1.704 - 4.084).

Table 1. Annualized spontaneous/unknown bleeding rate by age group (EU Categories, full analysis set, generalized linear model)

Regimen	Age Group [years]	Subjects Included in Analysis	Number of Bleeds Included in Analysis	Point Estimate	95% Confidence Interval
Fixed Dose Regimen, Twice Weekly at Time of Bleed	All	186	372	1.197	[0.918 - 1.561]
	Age <6	31	43	0.656	[0.394 - 1.094]
	Age ≥6 to <12	31	40	0.762	[0.438 - 1.325]
	Age ≥12 to <18	23	81	1.768	[1.093 - 2.859]
	Age ≥18	101	208	1.259	[0.876 - 1.812]
Fixed Dose Regimen, Every 5 Days at Time of Bleed	All	56	115	1.323	[0.873 - 2.006]
	Age <6	0	0	NA	NA
	Age ≥6 to <12	0	0	NA	NA
	Age ≥12 to <18	8	34	1.034	[0.498 - 2.147]
	Age ≥18	48	81	1.184	[0.741 - 1.894]
Fixed Dose Regimen, Every 7 Days at Time of Bleed	All	15	23	1.775	[0.776 - 4.056]
	Age <6	0	0	NA	NA
	Age ≥6 to <12	0	0	NA	NA
	Age ≥12 to <18	2	2	0.000	[0.000 - 0.000]
	Age ≥18	13	21	2.215	[0.914 - 5.368]
PK-tailored Regimen at Time of Bleed	All	25	35	0.964	[0.542 - 1.714]
	Age <6	4	4	0.915	[0.221 - 3.792]
	Age ≥6 to <12	6	9	0.874	[0.407 - 1.875]
	Age ≥12 to <18	6	6	0.842	[0.122 - 5.821]
	Age ≥18	9	16	1.006	[0.449 - 2.252]

Abbreviations: NA = not applicable; PK = pharmacokinetic(ally);
Point estimates and 95% confidence intervals obtained from a generalized linear model fitting a negative binomial distribution with logarithmic link function. Anti-logged results are presented for point estimates and confidence intervals. Separate models are fitted for the fixed every 5 days (q5d) and every 7 days (q7d) regimen including baseline age and previous ABR as fixed effects and the logarithm of follow-up time (in years) as offset. The twice weekly regimen and PK-tailored regimen are modeled together (separate from the q5d and q7d regimen) and include regimen and baseline age as fixed effects and the logarithm of follow-up time (in years) as offset.
A subject had to have 100 or more exposure days (across all studies) to be included in the analysis.
Subjects receiving dose in multiple regimens were included in summaries for multiple regimens.
Source: Table 47
Source: In-text Table 11, Report Body – Study 261302

Overall, the point estimate (95% CI) for the spontaneous ABR was comparable between subjects on a fixed-dose twice-weekly regimen and subjects on a PK-tailored prophylactic regimen, indicating that both regimens were equally effective in preventing spontaneous bleeds. Only select subjects qualified for prophylaxis administered q5d or q7d, based on their low spontaneous bleeding rate in the preceding 6-month period. It should be noted that any subject on an extended infusion interval who exceeded a defined frequency of spontaneous bleeds was to return to a shorter interval. As the extension or shortening of the treatment interval in these subjects was dependent on their bleeding rate, comparison with the other prophylactic regimens is not feasible.

Secondary efficacy outcome measures

Total Annualized Bleed Rate (ABR) including spontaneous and traumatic bleeding episodes

While on fixed-dose twice-weekly prophylaxis, 186 subjects had 686 bleeds. The point estimate (95% CI) for the total ABR was 2.230 (1.852 - 2.686). It was similar for subjects ≥18 years (2.166 [1.667 2.813]) and for subjects ≥6 to <12 years of age (1.997 [1.317 - 3.029]), lower for subjects aged <6 years (1.519 [1.037 - 2.225]), and higher for the ≥12 to <18 year age category (3.151 [2.256 - 4.401]).

Subjects who qualified for fixed-dose prophylaxis q5d (56) had a total of 194 bleeds while on this regimen. The point estimate (95% CI) for the total ABR on this regimen was 2.095 (1.537 - 2.855). It was similar for subjects ≥12 to <18 years and ≥18 years. No subjects <12 years were on this regimen.

Subjects who qualified for fixed-dose prophylaxis q7d (15) had a total of 43 bleeds while on this regimen. The point estimate (95% CI) for the total ABR on this regimen was 2.735 (1.437 - 5.204). It was lower for subjects ≥12 to <18 years (N = 2) (1.056 [0.185 - 6.041]) and higher for subjects ≥18 years (3.180 [1.535 - 6.590]). No subjects <12 years were on this regimen.

While on a PK-tailored regimen, 25 subjects included in the analysis had 103 bleeds. The point estimate (95% CI) for the total ABR was 2.638 (1.704 - 4.084). It was comparable in the ≥12 to <18 year age category (2.549 [0.653 - 9.954]) and in the <6 year age category (2.440 [0.712 - 8.362]), lower in the ≥18 year age category (1.381 [0.575 - 3.315]) and higher in subjects aged ≥6 to <12 years (4.979 [3.153 - 7.862]). In the 6 subjects aged ≥6 to <12 years, 40/49 bleeds were injury related; the point estimate (95% CI) for the injury-related ABR was 4.033 (2.637 -6.168).

Table 2. Annualized spontaneous/unknown bleeding rate by age group (EU Categories, full analysis set, generalized linear model)

Regimen	Age Group [years]	Subjects Included in Analysis	Number of Bleeds Included in Analysis	Point Estimate	95% Confidence Interval
Fixed Dose Regimen, Twice Weekly at Time of Bleed	All	186	686	2.230	[1.852 - 2.686]
	Age <6	31	88	1.519	[1.037 - 2.225]
	Age ≥6 to <12	31	101	1.997	[1.317 - 3.029]
	Age ≥12 to <18	23	136	3.151	[2.256 - 4.401]
	Age ≥18	101	361	2.166	[1.667 - 2.813]
Fixed Dose Regimen, Every 5 Days at Time of Bleed	All	56	194	2.095	[1.537 - 2.855]
	Age <6	0	0	NA	NA
	Age ≥6 to <12	0	0	NA	NA
	Age ≥12 to <18	8	59	2.238	[1.550 - 3.232]
	Age ≥18	48	135	1.879	[1.327 - 2.662]
Fixed Dose Regimen, Every 7 Days at Time of Bleed	All	15	43	2.735	[1.437 - 5.204]
	Age <6	0	0	NA	NA
	Age ≥6 to <12	0	0	NA	NA
	Age ≥12 to <18	2	7	1.056	[0.185 - 6.041]
	Age ≥18	13	36	3.180	[1.535 - 6.590]
PK-tailored Regimen at Time of Bleed	All	25	103	2.638	[1.704 - 4.084]
	Age <6	4	9	2.440	[0.712 - 8.362]
	Age ≥6 to <12	6	49	4.979	[3.153 - 7.862]
	Age ≥12 to <18	6	22	2.549	[0.653 - 9.954]
	Age ≥18	9	23	1.381	[0.575 - 3.315]

Abbreviations: NA = not applicable; PK = pharmacokinetic(ally).
Point estimates and 95% confidence intervals obtained from a generalized linear model fitting a negative binomial distribution with logarithmic link function. Anti-logged results are presented for point estimates and confidence intervals. Separate models are fitted for the fixed dose every 5 days (q5d) and every 7 days (q7d) regimen including baseline age and previous ABR as fixed effects and the logarithm of follow-up time (in years) as offset. The twice weekly regimen and PK-tailored regimen are modeled together (separate from the q5d and q7d regimen) and include regimen and baseline age as fixed effects and the logarithm of follow-up time (in years) as offset.
A subject had to have 100 or more exposure days (across all studies) to be included in the analysis.
Subjects receiving dose in multiple regimens were included in summaries for multiple regimens.
Source: Table 47
Source: In-text Table 12, Report Body – Study 261302

<u>Rate of Success of BAX 855 for Treatment of Bleeding Episode</u>

A total of 180/216 (83.3%) subjects had 1 or more bleeding episodes during the study. A total of 1064 bleeds occurred of which 910 in 165 subjects were treated and 154 were not treated with BAX 855. The subject or caregiver rated the severity (minor, moderate, or major) of the bleeding episode and the overall treatment response at 24 (±2) hours after the initiation of treatment using a 4-point efficacy rating scale ("excellent", "good", "fair", "none", "not reported").

Among a total of 910 treated bleeding episodes in 165 subjects, treatment of 48.1% (438) of bleeds was rated "excellent", treatment of 40.4% (368) of bleeds was rated "good", 5.3% (48) of bleed

treatments were rated "fair", and 0.4% (4) were rated "none"; for 5.7% (52) of bleed treatments no rating was reported.

Across age categories and for both the fixed-dose and the PK-tailored dose regimen, >85% of bleed treatments were rated "excellent" or "good". A majority of bleeds (673; 74.0%) was treated with 1 infusion, 15.4% (140) were treated with 2, 4.3% (39) were treated with 3, and 4.3% (39) were treated with ≥4 infusions; for 2.1% (19) of bleeding episodes, the information was not available. In both prophylactic regimens, the majority of bleeding episodes was treated with 1 infusion: 75.2% (611 of 813 treated bleeds that occurred in 158 subjects) while on a fixed-dose regimen and 63.7% (58 of 91 treated bleeding episodes that occurred in 15 subjects) while on a PK-tailored regimen. A mean (SD) of 1.4 (1.27) infusions was administered per bleeding episode; the mean number of infusions administered per bleed was 1.4 in all age categories. The total mean (SD) weight-adjusted dose per infusion to treat a bleed was 44.147 (21.919) IU/kg.

Overall, the proportion of bleed treatments rated "excellent" decreased with the severity of bleeds and the number of infusions to treat a bleed increased. Treatment was rated "excellent" for 60.1% (203/338) of bleeds of minor severity, 42.7% (198/464) of bleeds of moderate severity, and 36.6% (37/101) of bleeds of major severity. A mean (SD) of 1.1 (0.48) infusions was administered per minor bleed, a mean of 1.5 (1.17) infusions was administered per moderate bleed and a mean of 2.2 (2.52) infusions was administered per major bleed.

Time Intervals Between Bleeding Episodes

The overall mean (SD) interval between bleeding episodes was 6.429 (4.979) months (median: 5.495 months; range: 0.617; 22.686 months). The mean (SD) interval between bleeding episodes was similar for subjects on a fixed-dose prophylactic regimen (6.476 [4.999] months; median: 5.714 months; range: 0.617; 22.686 months). In subjects on a PK-tailored prophylactic regimen at the time of bleed, the (SD) interval between bleeding episodes was slightly lower at 4.033 (2.738) months (median: 2.947 months; range: 1.051; 9.550 months).

Number of BAX 855 Infusions Needed for the Treatment of Bleeding Episodes

In each EU age category and overall, a mean of 1.4 infusions and a median of 1.0 infusions were used to treat a bleed (range: 0 to 21). The mean (SD) total dose per bleed was 3979.2 (4382.33) IU (median [95% CI]: 3003.5 [3694.1 - 4264.3] IU).

In subjects on a fixed-dose prophylactic regimen at the time of bleed, a mean (SD) of 1.4 (1.27) infusions and a median (95% CI) of 1.0 (1.3 - 1.5) infusions were used to treat a bleed. The mean (SD) number of infusions was lower in the <6 year age category (1.2 [0.96]), the median number of infusions was 1.0 over all EU age categories.

In subjects on a PK-tailored prophylactic regimen at the time of bleed, a mean (SD) of 1.6 (1.24) infusions and a median (95% CI) of 1.0 (1.3 – 1.9) infusions were used to treat a bleed. The mean (SD) number of infusions was higher in the <6 year age category (4.3 [4.27]); in the other age categories it was similar to the number of infusions reported for all bleeds.

Weight-Adjusted Consumption of BAX 855

In subjects on a fixed-dose prophylactic regimen, the total mean (SD) weight-adjusted dose per infusion to treat a bleed was 43.873 (22.141) IU/kg (median [95% CI]: 44.600 [42.394 – 45.397] IU/kg). The mean (SD) weight-adjusted dose for the individual EU age categories ranged from 42.012 (24.809) IU/kg to 50.282 (18.424) IU/kg (median [95% CI]: 42.955 [39.797 - 44.228] IU/kg to 49.675 [46.208 - 54.356]). The mean (SD) total dose per bleed was 4043.8 (4491.68) IU (median [95% CI]: 3011.0 [3734.6 – 4353.1] IU).

In subjects on a PK-tailored prophylactic regimen, the total mean (SD) weight-adjusted dose per infusion to treat a bleed was 46.537 (20.443) IU/kg (median [95% CI]: 46.533 [42.279 - 50.794]

IU/kg). The mean (SD) weight-adjusted dose for the individual EU age categories ranged from 26.643 (1.904) IU/kg to 57.832 (12.263) IU/kg (median [95% CI]: 26.804 [25.776 - 27.509] IU/kg to 55.787 [38.318 - 77.345]). For all age categories except subjects ≥18 years, the mean weight-adjusted dose per infusion to treat a bleed was >50 IU/kg. The mean (SD) total dose per bleed was 3354.9 (3333.62) IU (median [95% CI]: 2118.0 [2660.7 - 4049.2] IU).

Patient Reported Outcomes (PROs)

Hemostatic efficacy of long-term treatment was reflected in PROs. Among the study population ≥18 years who completed the Haemo-SYM questionnaire at baseline and study completion, 56.8% (46/81) reported an improvement in the total Haemo-SYM score; improvement was significant at a p-value of 0.0006. Improvement of symptoms over baseline in the total Haemo-SYM score was observed both while on a fixed-dose regimen (N = 99) with a mean (SD) difference of -4.582 (13.326) and while on a PKtailored dose regimen (N = 9) with a mean (SD) difference of -12.778 (16.171). Both the pain severity and the bleed severity subscores improved during either prophylactic treatment regimen although 81.8% of subjects ≥18 years had already been on a prophylactic regimen prior to the study.

Health-related quality of life (HRQoL) was assessed using the Short Form 36 (SF-36) for subjects ≥14 years of age and the Pediatric Quality of Life Inventory (PedsQL) questionnaire for subjects <14 years. Overall, in the EU age categories (ages ≥12 to <18 years and ≥18 years), a total of 60.0% of subjects (57/95) who completed the SF-36 at baseline and study completion reported an improvement in the physical component score and 36.8% (35/95) reported an improvement in the mental component score. Improvement in the physical component score was significant at a p-value of 0.0005.

Overall, in the EU age categories (ages <6 years, ≥6 to <12 years, and ≥12 to <18 years), a total of 56.6% of subjects (30/53) who completed the PedsQL questionnaire at baseline and study completion reported an improvement in the total score. However, improvement did not reach statistical significance (p = 0.3256).

Safety results

A total of 218 subjects were enrolled in the study. 216 subjects received at least 1 prophylactic dose of BAX 855, including 121 adults, 30 adolescents, 33 children in the age group of 6 to <12 years of age and 32 children in the age group of <6 years of age. 215 subjects received at least one dose of BAX 855 at a fixed-dose prophylactic regimen and 25 subjects received at least one dose of BAX 855 at a PK-tailored prophylactic dose regimen (multiple treatment regimens were possible). The safety evaluation was performed on the FAS comprising these 216 subjects.

Exposure

Exposure to BAX 855 Prophylaxis

A total of 216 subjects received at least 1 infusion of BAX 855 in Study 261302. Exposure can be considered long-term at a mean of 209.8 (108.35) EDs per subject. The mean (SD) number of prophylactic EDs to BAX 855 was 195.4 (101.57). The number of exposure days to BAX 855 prophylaxis was slightly lower in patients <12 years than in the ≥12 years cohorts.

The mean (SD) weekly prophylactic BAX 855 infusion frequency over all 216 subjects was 1.735 (0.312); it was 1.722 (0.286) for the 215 subjects on a fixed-dose prophylactic regimen at any time during the study and slightly higher for subjects on PK-tailored prophylaxis at any time during the study at a mean (SD) of 2.113 (0.608). Prophylactic BAX 855 infusion frequency per week was similar over all age categories.

The mean (SD) weight-adjusted prophylactic dose per infusion as calculated for all subjects on prophylaxis was 51.363 (8.829) IU/kg. The weight-adjusted BAX 855 dose per prophylactic infusion was higher for paediatric patients <18 years than for adults ≥18 years. Doses ranged from 37.695 (12.311) IU/kg in subjects aged ≥18 years (N = 9) to 65.755 (15.223) IU/kg in subjects aged ≥12 to

<18 years (N = 6). The weight-adjusted dose per infusion was similar for subjects on fixed-dose prophylaxis at a mean (SD) of 51.149 (8.110) IU/kg and for subjects on PK-tailored prophylaxis at a mean (SD) dose of 52.137 (17.034) IU/kg.

The overall summary of exposure to BAX 855 prophylaxis by age group is presented in the table below.

Table 3. Exposure to BAX 855 prophylaxis by age group (EU Categories, safety analysis set)

Parameter	Statistics	Age <6	Age ≥6 to <12	Age ≥12 to <18	Age ≥18	Total
		Study Group: All				
Number of Subjects in Study Group	N	32	33	30	121	216
Average number of prophylactic infusions per week	n	32	33	30	121	216
	Mean (SD)	1.831 (0.339)	1.810 (0.194)	1.704 (0.358)	1.698 (0.313)	1.735 (0.312)
	Median	1.884	1.879	1.864	1.815	1.852
	Min; Max	0.534; 2.707	0.986; 2.111	1.011; 2.424	0.907; 3.084	0.534; 3.084
Average dose [IU/kg] per prophylactic infusion	n	32	33	30	121	216
	Mean (SD)	53.303 (7.569)	54.109 (8.224)	53.940 (10.588)	49.462 (8.447)	51.363 (8.829)
	Median	52.133	50.883	54.223	47.384	49.816
	Min; Max	41.281; 75.329	43.955; 73.348	39.686; 73.557	31.660; 80.304	31.660; 80.304
Exposure days to Prophylaxis	n	32	33	30	121	216
	Mean (SD)	173.1 (80.74)	181.7 (65.47)	202.9 (105.98)	203.2 (112.62)	195.4 (101.57)
	Median	185.5	199.0	213.5	213.0	208.5
	Min; Max	7; 333	42; 295	35; 477	18; 562	7; 562

Source: In-text Table 22, Report Body – Study 261302

Exposure to BAX 855 for Treatment of Bleeding Episodes
A total of 894 bleeding episodes were treated with BAX 855. The mean (SD) number of infusions to treat a bleeding episode was 1.5 (1.71) (median: 1.0; range: 1; 36). The mean (SD) weight-adjusted dose to treat a bleeding episode was 66.169 (70.646) IU/kg (median: 49.243 IU/kg; range: 0.000; 1084.950). The number of infusions and the weight-adjusted dose to treat a bleeding episode were similar for both treatment regimens and over all age categories. Only among the 4 subjects <6 years of age on a PK-tailored prophylactic regimen, the mean (SD) number of infusions and the weight-adjusted dose to treat a bleed were higher at 4.3 (4.27) and 269.108 (319.825) IU/kg, respectively. For a total of 71 bleeding episodes, BAX 855 was administered to maintain hemostasis. The mean (SD) number of infusions to maintain hemostasis was 1.7 (3.12) (median: 1.0; range: 1; 26). The mean (SD) weight-adjusted dose to maintain hemostasis was 73.103 (141.420) IU/kg (median: 48.077 IU/kg; range: 10.554; 1209.883 IU/kg).

The overall summary of exposure to BAX 855 for treatment of bleeding episodes by age group is presented in the table below.

Table 4. Exposure to BAX 855 for treatment of bleeding episodes by age group (EU Categories, safety analysis set)

Parameter	Statistics	Age <6	Age ≥6 to <12	Age ≥12 to <18	Age ≥18	Total
		Study Group: All				
Number of Subjects in Study Group	N	32	33	30	121	216
Average number of infusions to treat bleeding episode	n^a	66	125	197	506	894
	Mean (SD)	1.5 (1.46)	1.5 (0.86)	1.5 (1.69)	1.5 (1.90)	1.5 (1.71)
	Median	1.0	1.0	1.0	1.0	1.0
	Min; Max	1; 10	1; 5	1; 21	1; 36	1; 36
Average dose [IU/kg] to treat bleeding episode	n^a	66	125	197	506	894
	Mean (SD)	76.210 (93.372)	72.741 (40.942)	70.622 (82.025)	61.503 (68.022)	66.169 (70.646)
	Median	50.253	57.711	53.908	45.978	49.243
	Min; Max	19.305; 732.190	16.393; 227.004	0.000; 1019.161	12.819; 1084.950	0.000; 1084.950

Source: In-text Table 23, Report Body – Study 261302

Primary outcome measure

Development of Inhibitory Antibodies to FVIII

Development of inhibitory antibodies to FVIII (≥0.6 BU) was the primary safety outcome measure for this study. The analysis included subjects that developed inhibitory antibodies to FVIII and subjects that did not develop inhibitory antibodies to FVIII and had 100 or more EDs to BAX 855 across all studies and a FVIII inhibitory test result after the 100th exposure day.

None of the 204 subjects who qualified for the analysis (proportion: 0.000; 95% CI: 0.000 – 0.018) developed confirmed FVIII neutralizing antibodies during exposure to BAX 855.

One subject had a positive inhibitory antibody result to FVIII (0.6 BU), which was not confirmed at the second assessment. Inhibitors must be confirmed by 2 separate assessments within a 2 to 4 week period from the central laboratory. This subject was a 3-year-old Black/African American male, had a single positive FVIII inhibitor result of 0.6 BU in the Nijmegen assay performed at the central laboratory at 24 months (740 days after first BAX 855 infusion, 23 Oct 2017). After the initial positive inhibitor result, the subject could not return to the site for retesting within the 2 to 4 weeks stipulated in the protocol. On 2018 Jan 15, he returned for confirmatory testing. This visit was also considered the end-of-study visit as the trial was closing and the subject had more than 100 EDs to BAX 855, as required by the protocol. The inhibitor titer at retesting was negative (<0.4 BU). During the course of the study, the subject did not experience any symptoms or signs of inhibitor development. During an observation period of 2.256 years, the subject experienced one spontaneous minor bleeding episode on the skin, which resolved with one BAX 855 infusion. No SAEs and no AEs related to treatment with BAX 855 were reported for this subject. No IgG or IgM antibodies to FVIII, PEG-FVIII and PEG were observed at any time during the study.

Secondary outcome measure

Adverse Events

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A total of 838 AEs were reported for 174 (80.6%) subjects. This translates to 1.845 AEs/100 infusions and 1.761 AEs/year. The AEs (regardless of causality or seriousness) that were reported in the highest proportion of subjects were nasopharyngitis (18.5%), upper respiratory tract infection (11.6%), cough (9.3%), arthralgia (8.8%), headache (8.8%), pyrexia (7.4%) and diarrhoea (6%).

A total of 786 AEs in 167 (77.3%) subjects were **non-serious** (1.73 AEs/100 infusions; 1.652 AEs/year). The majority of the non-serious AEs were mild (586 in 86/216 [39.8%] subjects) or moderate (184 in 77/216 (35.6%) subjects). Fourteen AEs in 11/216 (5.1%) subjects were severe. Among the non-serious AEs, 20 in 11 (5.1%) subjects (0.044 AEs/100 infusions; 0.042 AEs/year) were considered related to BAX 855 by the investigator and 7 AEs in 4 subjects (1.9%) (0.015 AEs/100 infusions; 0.015 AEs/year) were assessed as being related to BAX 855 by the sponsor. All AEs assessed as related by the investigator were reviewed by the sponsor for assessment of causality. Different factors were considered in the assessment of causal relationship, including BAX 855 pharmacology, temporal relationship between onset of event and BAX 855 exposure, presence of any re-challenge and/or de-challenge experience, patients medical history, and use of concomitant medications. All related non-serious AEs were of mild or moderate severity. These related AEs included nausea, headache, eosinophil count increase and drug eruption. The incidence of each related AE was <1%.

The related AE of drug eruption was considered to represent a severe **hypersensitivity reaction**. The subject developed the mild event of drug eruption 1.1 days after exposure to BAX 855. Subsequent prophylactic infusions were administered as planned without any further reports of drug eruption or hypersensitivity reaction. The event was reported to have resolved approximately 3 to 4 weeks after study completion.

Subjects <6 years of age had a higher rate of non-serious AEs/100 infusions (2.944) and AEs/year (3.097). This appears to be largely attributable to higher rates of AEs in the system organ classes of infections and infestations, gastrointestinal disorders, and injury, poisoning and procedural complications in subjects <6 years compared to the overall subject population. However, the rate of related AEs was low at 0.034/100 infusions and 0.035/year.

Among a total of 838 AES in 174 subjects (80.6%), 52 AEs in 33 (15.3%) subjects were **serious** (0.114 AEs/100 infusions; 0.109 AEs/year). Among these, 5 SAEs in 5/216 (2.3%) subjects were mild, 20 SAEs in 11/216 (5.1%) subjects were moderate, and 27 AEs in 17/216 (7.9%) subjects were severe. The incidence of SAEs that occurred during or after first administration of BAX 855 was equally low across age groups and for the fixed-dose and PK-tailored prophylactic regimens. None of the SAEs were considered related to BAX 855 by the investigator or sponsor.

Table 5. Incidence of serious adverse events that occurred during or after first BAX 855 administration by age group (EU Categories, safety analysis set)

Study Group	Number of AEs n	Number of Subjects n (%)	AEs per 100 Infusions	AEs per Year
All (N=216/ I=45423/ Y=476)	52	33 (15.3)	0.114	0.109
Age <6 (N=32/ I=5944/ Y=57)	6	5 (15.6)	0.101	0.106
Age ≥6 to <12 (N=33/ I=6500/ Y=63)	7	2 (6.1)	0.108	0.111
Age ≥12 to <18 (N=30/ I=6661/ Y=71)	5	4 (13.3)	0.075	0.07
Age ≥18 (N=121/ I=26318/ Y=286)	34	22 (18.2)	0.129	0.119
Fixed Dose Regimen at Time of AE (N=215/ I=45172/ Y=473)	52	33 (15.3)	0.115	0.11
PK-tailored Regimen at Time of AE (N=25/ I=7221/ Y=63)	6	5 (20.0)	0.083	0.095

Abbreviations: n = number of subjects in each category; N = total number of subjects in the relevant analysis set, age group and study group; I = number of BAX 855 Infusions; Y = total observation period in years; % = percentage of subjects in each category relative to the number of subjects in the relevant analysis set, age group and study group.
AEs per 100 infusions derived as the number of AEs divided by total number of infusions, multiplied by 100.
AEs per year derived as the number of AEs divided by the observation period in years.
Subjects may be included in summaries for multiple study groups.
Source: Table 103 and Table 104

Source: In-text Table 29, Report Body – Study 261302

There was **one fatal SAE**, a cerebral hemorrhage in a 15-year-old Asian subject with radiologic findings suggestive of Moyamoya. The primary cause of death was intracerebral hemorrhage due to hemophilia; the event was considered unrelated to treatment with BAX 855. This subject, who had transitioned from the pivotal study, did not experience any prior AEs and no inhibitory or binding antibodies were detected in the course of the 271 EDs on twice-weekly BAX 855 prophylaxis in the continuation study. For all 3 bleeding episodes treated with BAX 855 in this subject (1 mild spontaneous joint bleed, 1 mild injury-related muscle bleed, and 1 moderate injury-related joint bleed), hemostatic efficacy was rated "excellent".

Four AEs in 2/216 (0.9%) subjects (0.009 AEs/100 infusions; 0.008 AEs/year) led to **discontinuation** of BAX 855, 8 AEs in 5/216 (2.3%) subjects (0.018 AEs/100 infusions; 0.017 AEs/year) led to discontinuation of study participation. Non-serious AEs leading to discontinuation included increased transaminases (2 subjects), ileus, traumatic fracture, a multiple hematomas, fracture of the right scapula and head injury. All AEs leading to discontinuation of BAX 855 or discontinuation of the study were reported from adult subjects ≥18 years. All AEs that led to withdrawal from the study were unrelated to treatment with BAX 855 per investigator assessment.

No subject reported a **thrombotic AE**.

<u>Development of Binding Antibodies to FVIII, PEG-FVIII, PEG and CHO Proteins</u>

Binding Ig (IgM, IgG, IgA) antibodies against CHO proteins (a potential impurity) and IgG and IgM antibodies against FVIII, PEG and PEG-FVIII were analyzed using ELISAs.

A total of 5 subjects (2 aged ≥6 to<12 years, 1 aged ≥12 to <18 years and 2 aged ≥18 years) had IgG binding antibodies to FVIII at any time post-baseline. However, antibodies were transient and had disappeared by the time of subject completion.

A total of 8 subjects (2 aged <6 years, 2 aged ≥6 to <12 years and 4 aged ≥18 years) had IgG binding antibodies to PEG-FVIII at any time post-baseline. Antibodies were transient and had disappeared by the time of subject completion in 4 of these subjects. One Subject (ID 251001), who

had transitioned from pivotal Study 261201, was positive for binding IgG antibodies to PEG-FVIII (1:160) at screening. Antibodies persisted at the same titer until the 12-month follow-up visit and at a titer of 1:320 at study completion. This subject, a 38 year-old Asian, (Subject 251002 in the pivotal study) had had pre-existing binding IgG antibodies to PEG-FVIII already at entry into the pivotal study, prior to first exposure to BAX 855. No IgG and IgM antibodies against FVIII and PEG and no IgM antibodies against PEG-FVIII were observed at any time during the continuation study or the prior pivotal study. There were no inhibitory antibodies against FVIII ≥0.6 BU/mL detected at any time during this study.

Three subjects developed binding IgG antibodies to both FVIII and PEG-FVIII at any time post-baseline. Both binding IgG antibodies to FVIII and to PEG-FVIII were transient in these subjects.

Clinical Laboratory Results

Hematology

For all parameters, the majority of subjects (50% or more) had normal values at baseline and subsequent visits. There were no clear trends for subjects who shifted from normal or abnormal NCS to clinically significant for any of the parameters.

The numbers of subjects with clinically significant shifts at completion were:

Table 6. Number of subjects with shifts in hematology laboratory assessments by prophylactic treatment regimen, from normal and abnormal not clinically significant at baseline to abnormal clinically significant at completion/termination (safety analysis set)

Parameter	Number of Subjects	
	From Normal n	**From Abnormal NCS** n
Fixed-dose Regimen (N=214)		
Eosinophils/Leukocytes	1	0
Ery. Mean Corpuscular Volume (fL)	1	1
Erythrocytes (10^12/L)	0	1
Hematocrit (v/v)	1	2
Hemoglobin (g/L)	1	1
Leukocytes (10^9/L)	1	0
Lymphocytes/Leukocytes	1	0
Platelets (10^9/L)	1	0
PK-tailored Regimen (N=25)		
Hematocrit (v/v)	1	0
Hemoglobin (g/L)	1	0

Abbreviations: NCS = not clinically significant; N = total number of subjects in the relevant analysis set; n = number of subjects in each category; PK = pharmacokinetic(ally).
Baseline defined as the last non-missing measurement obtained prior to first BAX 855 administration in the continuation study. Subjects receiving dose in both the fixed dose and PK-tailored regimens were included in summaries for both study groups.
Source: Table 121, Table 122

Source: In-text Table 32, Report Body – Study 261302

Clinical chemistry

For all parameters, the majority of subjects (50% or more) had normal values at baseline and subsequent visits. There were no clear trends for subjects who shifted from normal or abnormal NCS to clinically significant for any of the parameters. No shifts from normal or abnormal NCS at baseline to abnormal clinically significant at completion were observed in subjects while on the PK-tailored regimen (N=25).

The numbers of subjects with clinically significant shifts at completion, while on a fixed-dose regimen were:

Table 7. Number of subjects with shifts in clinical chemistry laboratory assessments by prophylactic treatment regimen, from normal and abnormal not clinically significant at baseline to abnormal clinically significant at completion/termination (safety analysis set)

Parameter	Number of Subjects	
	From Normal n	**From Abnormal NCS** n
Fixed-dose Regimen (N=214)		
Alanine Aminotransferase (U/L)	2	1
Alkaline Phosphatase (U/L)	3	0
Aspartate Aminotransferase (U/L)	1	1
Bilirubin (µmol/L)	0	1
Glucose (mmol/L)	1	0

Abbreviations: NCS = not clinically significant; N = total number of subjects in the relevant analysis set; n = number of subjects in each category.
Baseline defined as the last non-missing measurement obtained prior to first BAX 855 administration in the continuation study. Subjects receiving dose in both the fixed dose and PK-tailored regimens were included in summaries for both study groups.
Source: Table 123, Table 124

Source: In-text Table 31, Report Body – Study 261302

Lipids

For all parameters, the majority of subjects (50% or more) had normal values at baseline and subsequent visits. There were some transient shifts which normalized by the end of the study, so no trends in lipid laboratory results were detected.

The numbers of subjects with clinically significant shifts from baseline at completion were:

Table 8. Number of subjects with shifts in lipid panel assessments by prophylactic treatment regimen, from normal and abnormal not clinically significant at baseline to abnormal clinically significant at completion/termination (safety analysis set)

Parameter	Number of Subjects	
	From Normal n	From Abnormal NCS n
Fixed-dose Regimen (N=214)		
Cholesterol (mmol/L)	2	0
HDL Cholesterol (mmol/L)	1	0
LDL Cholesterol (mmol/L)	2	0
Triglycerides (mmol/L)	2	1
VLDL Cholesterol (mmol/L)	2	0
PK-tailored Regimen (N=25)		
VLDL Cholesterol (mmol/L)	2	0

Abbreviations: NCS = not clinically significant; N = total number of subjects in the relevant analysis set; n = number of subjects in each category; PK = pharmacokinetic(ally); HDL = high density lipoprotein; LDL = low density lipoprotein; VLDL = very low density lipoprotein.
Baseline defined as the last non-missing measurement obtained prior to first BAX 855 administration in the continuation study. Subjects receiving dose in both the fixed dose and PK-tailored regimens were included in summaries for both study groups.
Source: Table 125, Table 126

Source: In-text Table 33, Report Body – Study 261302

Vital Sign Measurements, Physical Examination Findings, and other Observations related to safety

There were no clear trends in vital signs over time during long-term exposure to prophylaxis with BAX 855.

2.3.3. Discussion on clinical aspects

The MAH submitted an Article 46 of the Paediatric Regulation submission, containing the final Clinical Study Report of study 261302. A subset of the patient population in the study are paediatric subjects, so this submission is done to meet the requirement of Art. 46 to submit paediatric data within 6 months from End of Study.

Overall exposure of at least 100 EDs for each subject was carried out and hence, the study conduct is in line with the "Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products" (EMA/CHMP/BPWP/144533/2009).

The extension trial, study 261302, was performed to evaluate the long-term safety and efficacy of BAX 855 in prophylactic use and the treatment of bleeding episodes in adult and pediatric subjects with severe hemophilia A who either transitioned from other BAX 855 studies or were newly recruited.

A total of 218 subjects were enrolled, of whom 216 subjects received at least 1 prophylactic dose of BAX 855. 215 subjects received at least one dose of BAX 855 at a fixed-dose prophylactic regimen and 25 subjects received at least one dose of BAX 855 at a PK-tailored prophylactic dose regimen (multiple treatment regimens were possible).

The co-primary objectives of the study were to determine the safety of BAX 855 based on the incidence of FVIII inhibitory antibody development and to determine efficacy based on the annualized spontaneous bleeding rate. Secondary objectives included total annualized bleeding rate (ABR), efficacy of treatment of bleeding episodes, number of infusions to treat bleeding episodes, time interval between bleeds, weight-adjusted consumption of BAX 855, and patient-reported outcomes (PROs). Secondary safety objectives included occurrence of adverse events (AEs), changes in vital signs and clinical laboratory parameters and immunogenicity of BAX 855.

Most subjects were ≥18 years of age (n= 121), 30 subjects were ≥12 to <18 years of age, 33 subjects were 6 to < 12 years of age and 32 subjects were <6 years of age.

Conclusion on Efficacy:

Spontaneous annualized bleeding rate

The point estimate for the spontaneous ABR for subjects on fixed-dose, twice-weekly, q5d or q7d prophylaxis was 1.197 (0.918 - 1.561), 1.323 (0.873 - 2.006) and 1.775 (0.776 - 4.056), respectively. The point estimate for the spontaneous ABR for subjects on a PK-tailored regimen was 0.964 (0.542 - 1.714). All subjects on either q5d or q7d regimen were ≥12 years of age.

Total Annualized Bleed Rate (ABR) including spontaneous and traumatic bleeding episodes

The mean (SD) total ABR for all subjects on prophylaxis (n=216), was 2.492 (3.116). The mean (SD) total ABR was similar in subjects while on a fixed-dose prophylactic regimen (N = 215) at 2.450 (3.153) and while on a PK-tailored prophylactic regimen (N = 25) at 2.615 (3.291). The point estimate (95% CI) for the total ABR in subjects on twice-weekly prophylaxis, q5d or q7d was 2.230 (1.852 - 2.686), 2.095 (1.537 - 2.855) and 2.735 (1.437 - 5.204). Subjects on a PK-tailored prophylactic regimen had a point estimate for total ABR of 2.638 (1.704 - 4.084). The overall total ABR was comparable across age categories except subjects aged ≥12 to <18 years (N = 30). In this age group the total ABR was higher at a mean (SD) of 3.163 (2.673), comparable with the preceding studies, where also the total ABRs was higher in adolescents than in the other analysis populations.

Overall, spontaneous, total ABRs and dosing intervals during twice-weekly prophylaxis and subjects on PK-tailored prophylaxis were in a range similar to those observed over the course of the preceding phase 3 trials.

Rate of Success of BAX 855 for Treatment of Bleeding Episode

The severity (minor, moderate, or major) of a bleeding episode and the overall treatment response at 24 (±2) hours after the initiation of treatment was rated by the subject or caregiver using a 4-point efficacy rating scale ("excellent", "good", "fair", "none", "not reported"). Among a total of 910 treated bleeding episodes in 165 subjects, treatment of 48.1% (438) of bleeds was rated "excellent", treatment of 40.4% (368) of bleeds was rated "good", 5.3% (48) of bleed treatments were rated "fair", and 0.4% (4) were rated "none"; for 5.7% (52) of bleed treatments no rating was reported. To summarize, similar to the parent studies, the majority of BEs were treated with 1 infusion: 75.2% (611 of 813 treated bleeds that occurred in 158 subjects) while on a fixed-dose regimen and 63.7% (58 of 91 treated bleeding episodes that occurred in 15 subjects) while on a PK-tailored regimen.

Time Intervals Between Bleeding Episodes

The overall mean (SD) interval between bleeding episodes was 6.429 (4.979) months (median: 5.495 months; range: 0.617; 22.686 months). The mean (SD) interval between bleeding episodes was similar for subjects on a fixed-dose prophylactic regimen (6.476 [4.999] months; median: 5.714 months; range: 0.617; 22.686 months). In subjects on a PK-tailored prophylactic regimen at the time of bleed, the (SD) interval between bleeding episodes was slightly lower at 4.033 (2.738) months (median: 2.947 months; range: 1.051; 9.550 months). It was longest in subjects ≥18 years of age (7.217 [5.764] months; N = 80) and ranged between 4.852 (2.981) months and 5.837 (3.777) months in younger subjects

Number of BAX 855 Infusions Needed for the Treatment of Bleeding Episodes

In each EU age category and overall, a mean of 1.4 infusions and a median of 1.0 infusions were used to treat a bleed (range: 0 to 21). The mean (SD) total dose per bleed was 3979.2 (4382.33) IU (median [95% CI]: 3003.5 [3694.1 - 4264.3] IU).

In subjects on a fixed-dose prophylactic regimen at the time of bleed, a mean (SD) of 1.4 (1.27) infusions and a median (95% CI) of 1.0 (1.3 - 1.5) infusions were used to treat a bleed. The mean (SD) number of infusions was lower in the <6 year age category (1.2 [0.96]), the median number of infusions was 1.0 over all EU age categories.

In subjects on a PK-tailored prophylactic regimen at the time of bleed, a mean (SD) of 1.6 (1.24) infusions and a median (95% CI) of 1.0 (1.3 – 1.9) infusions were used to treat a bleed. The mean (SD) number of infusions was higher in the <6 year age category (4.3 [4.27]); in the other age categories it was similar to the number of infusions reported for all bleeds.

Weight-Adjusted Consumption of BAX 855

For subjects who enrolled from Study 261302, the total mean±SD weight-adjusted dose per infusion of BAX 855 to treat a bleed during the efficacy period was 43.873 (22.141) IU/kg (median [95% CI]: 44.600 [42.394 – 45.397] IU/kg). The mean (SD) weight-adjusted dose for the individual EU age categories ranged from 42.012 (24.809) IU/kg to 50.282 (18.424) IU/kg (median [95% CI]: 42.955 [39.797 - 44.228] IU/kg to 49.675 [46.208 - 54.356]). The mean (SD) total dose per bleed was 4043.8 (4491.68) IU (median [95% CI]: 3011.0 [3734.6 – 4353.1] IU).

In subjects on a PK-tailored prophylactic regimen, the total mean (SD) weight-adjusted dose per infusion to treat a bleed was 46.537 (20.443) IU/kg (median [95% CI]: 46.533 [42.279 - 50.794] IU/kg). The mean (SD) weight-adjusted dose for the individual EU age categories ranged from 26.643 (1.904) IU/kg to 57.832 (12.263) IU/kg (median [95% CI]: 26.804 [25.776 - 27.509] IU/kg to 55.787 [38.318 - 77.345]). For all age categories except subjects ≥18 years, the mean weight-adjusted dose per infusion to treat a bleed was >50 IU/kg. The mean (SD) total dose per bleed was 3354.9 (3333.62) IU (median [95% CI]: 2118.0 [2660.7 - 4049.2] IU).

To conclude, consumption of BAX 855 in the extension study appears to be similar to that in the preceding studies.

Overall the efficacy data generated in the continuation study 261302 are broadly comparable with the respective results obtained in the studies submitted for MAA indicating that Adynovi is effective for the prophylaxis of bleeding episodes in patients aged 12 years and above with severe hemophilia A.

Conclusion on Safety:

The Safety Analysis Set comprises 216 who received at least 1 dose of BAX 855 during the study.

The primary outcome measure of this study was the development of FVIII inhibitors. None of the subjects developed confirmed FVIII neutralizing antibodies during BAX 855 exposure. Only one subject had a positive inhibitory antibody result to FVIII (0.6 BU), which was not confirmed at the second assessment. A total of 838 AEs occurred in 174 (80.6%) subjects treated with BAX 855, of which 52 in 33 subjects (15.3%) AEs in subjects were reported to be serious. Among the non-serious AEs, 20 in 11 (5.1%) subjects were considered related to BAX 855 by the investigator and 7 AEs in 4 subjects (1.9%) were assessed as being related to BAX 855 by the sponsor. The AEs assessed as related by the sponsor included nausea, headache, eosinophilia and drug eruption. However, the AEs considered as being related by the investigator but assessed as not related by the sponsor are not adequately justified and need to be discussed in this context. Subjects <6 years of age had a higher rate of non-serious AEs. However, the rate of related AEs was lower in this paediatric subset compared to the overall subject population.

There was one fatal outcome, a cerebral haemorrhage in a 15-year-old Asian subject who had radiologic findings suggestive of Moyamoya. This subject, who had transitioned from a previous study, did not experience any prior AEs and no inhibitory or binding antibodies were detected in the course of the 271 EDs on twice-weekly BAX 855 prophylaxis in the continuation study. This SAE was considered as not related to the study product. No additional safety concerns arise from this event with fatal outcome.

Four AEs in 2 (0.9%) subjects led to discontinuation of BAX 855, 8 AEs in 5 (2.3%) subjects led to discontinuation of study participation. However, all AEs leading to discontinuation were reported from adult subjects ≥18 years and assessed as being not related to BAX 855 treatment.

A total of 5 subjects had IgG binding antibodies to FVIII at any time post-baseline and 8 subjects had IgG binding antibodies to PEG-FVIII at any time post-baseline. Binding antibodies to FVIII and PEG-FVIII were transient in all but one subject. This subject who had transitioned from pivotal Study 261201 had pre-existing binding IgG antibodies to PEG-FVIII already at entry into the pivotal study, prior to first exposure to BAX 855, which persisted throughout the studies. No conspicuous safety or efficacy results were reported from this subject during the study.

To summarize, review of safety data from Study 261302 did not reveal unusual findings or new safety signals for BAX 855. Overall, from the data set provided, safety and tolerability of BAX 855 in children, adolescents and adults seem to be comparable with the data generated in the parent studies. No new safety aspects other than those observed in the course of the MAA became apparent.

3. Rapporteur's overall conclusion and recommendation

The MAH submitted the final clinical study report of the continuation study 261302. A short critical overview was also included. The data presented in the final study report did not indicate any new safety or efficacy aspects that may alter the benefit risk profile. The benefit risk profile therefore remains positive in the licenced indication for patients aged 12 years and above. The MAH concludes that data do not require an update of the Product Information. This can be supported since the information obtained in the final study report is already covered by the currently approved PI.

Additional clarification regarding the causality assessment of AEs has been provided by the Applicant. Among the non-serious AEs, 20 AEs in 11 (5.1%) subjects were considered to be related to BAX 855 by the investigator and 7 AEs in 4 subjects (1.9%) were considered to be related by the sponsor. The Applicant submitted brief narrative descriptions for each subject who experienced an AE that has been assessed as related by the investigator but not considered related by the sponsor and provided the requested discussion on the causality assessment of these AEs. Review of the individual case reports revealed no clear evidence for a relation of these AEs with BAX 855 treatment. The Applicant had

satisfactorily clarified and discussed this issue. No new safety concerns arise from these additional data.

☒ **Fulfilled:**

☐ **Not fulfilled:**

No regulatory action required.

4. Additional clarification requested

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

Among the non-serious AEs, 20 AEs in 11 (5.1%) subjects were considered to be related to BAX 855 by the investigator and 7 AEs in 4 subjects (1.9%) were considered to be related by the sponsor. The AEs assessed as related by the sponsor included nausea, headache, eosinophilia and drug eruption. Three of these AEs (nausea, headache and drug eruption/hypersensitivity) are adequately reflected in section 4.8 of the SmPC. However, the AEs considered as being related by the investigator but assessed as not related by the sponsor are not adequately justified and a thorough discussion should be provided. Additionally, the Applicant should provide the narrative of the patient who experienced the AE of eosinophilia considered to be related to BAX 855 by both the investigator and the sponsor.

The timetable is a 30 day response timetable without clock stop.

MAH responses to Request for supplementary information

Applicant´s response

1. Discussions about the AEs assessed as related by the investigator but considered not

related by the sponsor:

HIGH DENSITY LIPOPROTEIN

Subject 125001 had an increased HDL level of 2.25 mmol/L (reference range: 0.98-1.94 mmol/L) for pre-infusion lab test at 6-month visit on 16 Mar 2016, which was reported as a mild AE and was considered as possibly related to BAX 855 by the investigator. The subject's last infusion of BAX 855 before this pre-infusion lab test was 6 days earlier on 10 Mar 2016, and the HDL level returned to normal at the next visit (the End of Study visit) on 8 Jun 2016 without being treated by any concomitant medications in the context of a continued IP prophylaxis. Therefore, this transient increase in HDL is not considered as related to BAX 855.

OTITIS MEDIA

Subject 125002 had 2 moderate AEs of otitis media (right otitis media and left otitis media) that were assessed as possibly related to BAX 855 by the investigator. The sponsor assessed it as unrelated because it was considered to be related to the reported ongoing pre-existing condition eustachian tube dysfunction, and there is no biological plausibility to BAX 855 infusions. The subject also had non-serious AEs of left ear pain, otitis externa and bilateral ear pain during the study and they were all assessed as unrelated by the investigator.

MONOCYTE COUNT DECREASED

Subject 255002 had a mild AE of low monocyte count, which was assessed as possibly related to BAX 855 by the investigator. This abnormal lab value was reported from screening lab test on 22 Jun 2017, and it actually was an AE continued from the previous BAX 855 study (261303) the subject participated and was recorded in the subject's medical history in this continuation study, and the AE reported in study 261303 was assessed by the investigator as unrelated. In addition, without any treatment, the AE was resolved, the value turned out to be normal at the next visit (6-week visit) on 10 Aug 2017. Therefore, the sponsor considered it as unrelated to the IP.

HEADACHE

Subject 390001 had 2 occurrences of moderate AEs of headache that were assessed as possibly related to BAX 855 by the investigator but as unrelated by the sponsor. Both AEs occurred after 24 hours of IP infusion, the sponsor consider that they are unlikely to be related to BAX 855 due to their temporal relationship to administration.

UPPER RESPIRATORY TRACT INFECTION

Subject 390001 experienced a moderate AE of upper respiratory tract infection (URTI) on 24 Dec 2014 within 24 hour of BAX 855 treatment and it was considered as possibly related by the investigator. However, given multiple respiratory system infection conditions including pneumonia, cough, cold, flu reported in the medical history, and that the subject had another AE of URTI on 17 Sep 2014 that was assessed as unlikely related, the sponsor assessed this AE as not related to BAX 855.

ALANINE AMINOTRANSFERASE INCREASED

Subject 391001 had a significantly increased ALT level of 64 U/L (reference range: 6-43 U/L) for pre-infusion lab test at the Week 6 visit on 12 Aug 2014, which was reported as a moderate AE and was considered as probably related to BAX 855 by the investigator. The subject was tested positive for Hepatitis B virus surface antibodies at screening. He also had a transient increase of AST to 43 IU/L at the Week 6 visit. On 27 Aug 2014, an unscheduled lab test was performed for the AE assessment purpose and the result of ALT was normal (39 U/L). There was no action taken for the AE and the IP infusion was not changed. The subject's last infusion of BAX 855 before this pre-infusion lab test was 4 days earlier on 8 Aug 2014. Based on the transient nature and the time to event onset, the sponsor assessed this AE as not related to BAX 855.

HYPERBILIRUBINAEMIA

Subject 400001 had a moderate AE of hyperbilirubinemia and it was assessed as possibly related to BAX 855 by the investigator. This AE was continued from the previous BAX 855 study the subject participated in (study 261201), the elevated total bilirubin level was detected on 27 Jan 2014 at screening (37 μmol/L, reference range: 3-21 μmol/L) visit, which was the completion/termination visit of study 261201. In 261201 the AE was assessed by the investigator as possibly related, however, the subject has stable HBV and

HCV infection reported in his medical history with fluctuating total bilirubin levels ranging from 25 μ mol/L at screening of 261201, returning to normal ranges at Week 2 and Week 4 and increasing to 37 μ mol/L at completion/termination, returning to normal at 1 month visit in this continuation study. These fluctuations are in line with stable HCV and therefore not related to BAX 855. The subject was withdrawn from the study on 31MAR2014, and the early termination is not related to the reported AEs.

DYSLIPIDAEMIA

Subject 400002 had a mild AE of dyslipidaemia and it was considered as possibly related to BAX 855 by the investigator. The subject had been having high or borderline cholesterol levels since the screening visit, and there were transient abnormal high levels of triglycerides and VLDL at Month 24 visit. Given that it is an isolated case reported across the study and it was resolved without being treated by any concomitant medications in the context of a continued study IP treatment, the sponsor assessed as unrelated to BAX 855.

EOSINOPHIL COUNT INCREASED

Subject 527001 had a mild AE of high eosinophils (start date of 04 Apr 2016,), which was based on the Month 21 visit eosinophils (%) lab test result of 31.6% (reference range: 0-2.8%). It was assessed as possibly related to BAX 855 by the investigator.

However, the subject had been having greatly elevated eosinophil levels detected since screening visit (20.9%), therefore the sponsor considered it as unrelated to BAX 855.

HAEMOPTYSIS and UPPER RESPIRATORY TRACT INFECTION

Subject 527001 had AEs of haemoptysis and upper respiratory tract infection for which causality was not assessed by the investigator and were conservatively counted towards related AEs in the clinical report. The AEs took place on 28 Apr 2017 with unknown time, the last infusion before the AEs' onset was on 27 Apr 2017. Taking into account the factors of time to event onset and consistent trend in studies as well as biological plausibility, the sponsor considered them as unrelated to BAX 855.

2. <u>Narrative of the patient who experienced the AE of eosinophilia considered to be related to BAX 855 by both the investigator and the sponsor.</u>

Subject 491001 had 3 cases of mild AEs of increased eosinophils count (Nov2015- 25Aug2016, 08Nov2016-16Feb2017, and 01Jun2017-unresolved) and they were all assessed as possibly related to BAX 855 by the investigator. The subject had been having elevated eosinophils since the 6-month visit (04Nov2014), the investigator suspected they were allergic reactions to BAX 855. There were no change of IP dose or other actions taken for the AE and the subject completed the study on 13Nov2017 without a resolution of the AE. Although the first occurrence of the AE was after more than

24 hours from the last BAX 855 infusion, the sponsor considered that a possible association cannot be ruled out, and therefore has conservatively assessed them as related to BAX 855.

Assessment of Response:

The Applicant submitted brief narrative descriptions for each subject who experienced an AE that has been assessed as related by the investigator but not considered related by the sponsor and provided the requested discussion on the causality assessment of these AEs.

Review of the individual case reports revealed no clear evidence of these AEs to be related to BAX 855 treatment. It is agreed with the sponsor that the temporal relationship and the transient nature of some of these AEs (e.g. headache, ALT increase) as well as pre-existing conditions in some subjects (e.g. eosinophil count increase, otitis media) do not support a causal relationship between these AEs and treatment with BAX 855.

Additionally, the Applicant provided the requested case narrative of the patient who experienced the AE of eosinophilia considered treatment related by both the investigator and the sponsor. The subject had elevated eosinophils since the 6-month visit and the investigator suspected that the AE of increased eosinophils is attributed to allergic reactions to BAX 855. No change of BAX 855 dose or other actions have been taken and the subject completed the study (without a resolution of this AE). The AE of hypersensitivity or allergic reactions are adequately reflected in section 4.8 of the SmPC.

The Applicant had satisfactorily clarified and discussed this issue. No new safety concerns arise from these additional data.

Issue resolved.