Evaluation of Long-Term Prophylaxis With A Pegylated Full-Length Recombinant Factor VIII With Extended Half-Life In Patients With Hemophilia A

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INTRODUCTION

- Patients with severe hemophilia A have < 1% of normal factor VIII (FVIII) levels and experience frequent bleeding, which can be prevented by prophylaxis with FVIII replacement.[1]
- BAX 855, a polyethylene glycol (peg)ylated, full-length, recombinant FVIII (rFVIII), is built on the plasma/albumin-free manufacturing platform of rAHF-PFM (ADVATE). Controlled pegylation was chosen to extend the FVIII half-life while maintaining the integrity of the ADVATE protein.[2]
- A first-in-human phase 1 clinical study with BAX 855 demonstrated that the half-life in the circulation is extended by up to 1.5 times compared to ADVATE and that single infusions were well tolerated.[3]
- The BAX 855 pivotal study confirmed the extended half-life of BAX 855 and demonstrated the efficacy and safety of BAX 855 for prophylaxis and for the treatment of bleeding in previously treated adolescents and adults with severe hemophilia A.[4]
- The BAX 855 pediatric study demonstrated the safety and efficacy of BAX 855 for prophylaxis and for the treatment of bleeding episodes in previously treated children with severe hemophilia A which included confirmation of its extended half-life.[5]
- The BAX 855 surgery study demonstrated the safety and efficacy of BAX 855 for perioperative management.[6]
- Patients from these studies could continue prophylactic treatment in the BAX 855 continuation study.

OBJECTIVE

- Data from the BAX 855 clinical program (3 completed and 2 ongoing studies) were integrated to evaluate the efficacy of long-term twice weekly prophylaxis and to explore reducing the dosing frequency. For the evaluation of long-term prophylaxis, 3 of the studies were included; pivotal, pediatric, and continuation (refer to Table 1).

METHODS

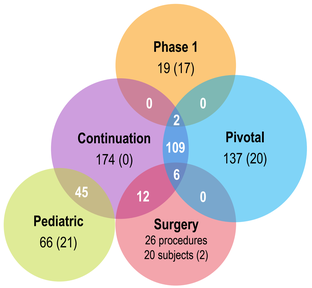
Table 1: BAX 855 Studies

Description	IDs for ClinicalTrials.gov clinicaltrialsregister.eu	Study Status	Planned Treatment
Phase 1: Pharmacokinetics (PK), single infusion tolerability	NCT01599819	Complete	PK: 30 or 60 ± 5 IU IU/kg
***Pivotal**: Phase 2/3, PK, efficacy, safety, immunogenicity	NCT01736475 EudraCT 2012-003599-38	Complete	PK: 45 ± 5 IU/kg Prophylaxis: 45 ± 5 IU/kg twice weekly On-demand treatment: 10 to 60 ± 5 IU/kg
***Pediatric**: Phase 3, PK, efficacy, safety, immunogenicity	NCT02210091 EudraCT 2014-000742-30	Complete	Prophylaxis: 50 ± 10 IU/kg twice weekly PK: 60 ± 5 IU/kg
Surgery: Phase 3, perioperative hemostasis, safety	NCT01913405 EudraCT 2013-001359-11	Ongoing	Tailored dose to achieve FVIII target levels for: Major procedures: 80% to 100% of normal Minor procedures: 30% to 60% of normal
***Continuation**: Phase 3b, long-term efficacy, safety, immunogenicity	NCT01945593 EudraCT 2014-005477-37	Ongoing	Refer to Figure 2

*Studies included in the evaluation of long-term prophylaxis

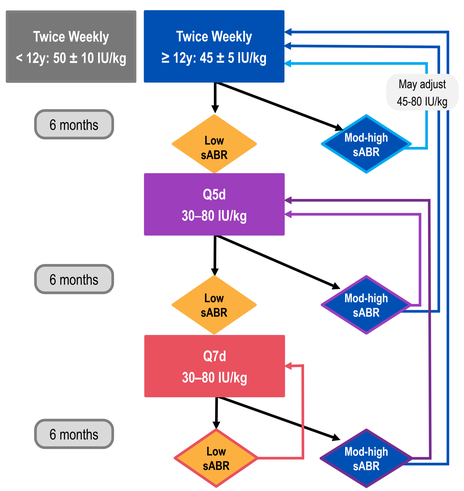
METHODS continued

Figure 1: Patient Disposition - 234 Treated Patients, 215 on Prophylaxis



- N (n): Number of patients treated in the study (number of patients unique to that study); others were treated in 1 or more studies
- Data from the pivotal, pediatric, and continuation studies were included in the evaluation of long-term prophylaxis

Figure 2: Prophylactic Treatment Regimens in the Continuation Study – Options for Reducing the Dosing Frequency for Adolescents and Adults with Low Annualized Bleeding Rates



Abbreviations: ABR, annualized bleeding rate; sABR, spontaneous ABR; Mod, moderate; Q5d, every 5 days; Q7d, every 7 days; y, years of age

- In a protocol amendment, these treatment options were revised to twice weekly fixed dose (45 ± 5 IU/kg for adolescents and adults ≥ 12 years and 50 ± 10 IU/kg for children < 12 years) prophylaxis or PK-tailored prophylaxis targeting ≥ 3% FVIII trough levels. However, subjects on Q5d and Q7d prophylaxis at the time of the amendment could remain on these regimens until study completion. Because of the timing of the amendment, no children from the pediatric study who continued were treated on the Q5d or Q7d regimens.

Statistical Model

- ABRs (total, spontaneous, and joint) were assumed to have a negative binomial distribution, and the mean (95% CI) was estimated using a generalized linear model rather than the planned general estimating equation model framework (with a logarithmic link function which is the default for the negative binomial distribution). This model took into account the treatment regimen (as a fixed effect), patients (as a random effect), age at baseline (as a continuous covariate), and follow-up time (as an offset).

RESULTS

Demographics

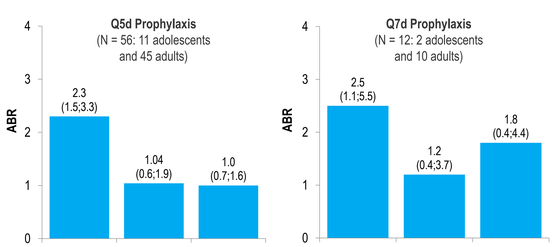
- **Age**: The mean ±SD (minimum to maximum) age is 23.6 ±15.4 (1 to 60) years of age.
- **Gender**: One patient was female and the remaining were male.
- **Race**: Most (74.4%) were White, 21.8% were Asian, 2.6% were Black, and the remaining 0.9% were of other race(s).

Table 1: Overall Treatment by Age Group Over the Entire Period

	Average* Infusions per Week	Average* Dose (IU/kg) per Infusion
All Ages	1.7	48.3
Younger Children (< 6 years)	1.8	51.3
Older Children (6 to < 12 years)	1.8	51.2
Adolescents (12 to < 18 years)	1.6	47.7
Adults (≥ 18 years)	1.7	46.9

*Includes all treatment regimens, ie twice weekly, Q5d, Q7d, and PK-tailored over 1 or more study periods.

Figure 3: Mean (Q1;Q3) Annualized Bleeding Rate Point Estimates



- For 215 patients on twice weekly prophylaxis (included 66 children, 26 adolescents, and 123 adults), point estimates for mean (95% confidence intervals) ABR were 4.7 (3.9-5.7) for total, 2.9 (2.3-3.7) for joint, and 2.0 (1.6-2.6) for spontaneous bleeding. These estimates seem higher because this analysis also included patients with more severe bleeding phenotypes who remained on twice weekly prophylaxis (refer to Figure 2). Reported median ABRs for children were 2.0 for total bleeding and 0 for joint and spontaneous bleeding,[5] and for adolescents and adults median ABRs were 1.9 for total bleeding and 0 for joint and spontaneous bleeding.[4]

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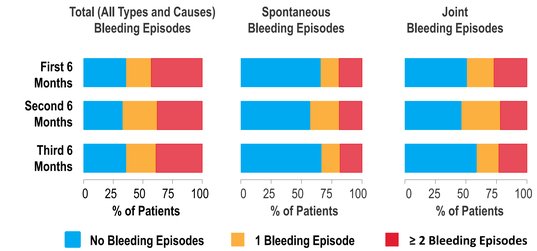
RESULTS continued

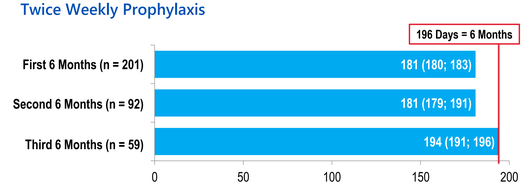
Figure 4: Percent of Patients with Bleeding Episodes Over Time on Twice Weekly Prophylaxis

- First 6 Months (n = 201): 63 children, 24 adolescents, and 114 adults
- Second 6 Months (n = 92): 14 adolescents and 78 adults
- Third 6 Months (n = 59): 11 adolescents and 48 adults



- 36% of patients had no bleeding episodes during the first 6 months of twice weekly prophylaxis with BAX 855, and this was maintained over consecutive 6-month treatment periods.
- 66% of patients had no spontaneous bleeding episodes during the first 6 months, which was maintained over consecutive 6-month treatment periods.
- 51% of patients had no joint bleeding episodes, which was also maintained.
- For number of patients and age groups included, refer to Figure 3.

Figure 5: Intervals (in Days) Between Bleeding Episodes Over Time on Twice Weekly Prophylaxis



- The median time between bleeding episodes (181 days of a 196-day period) while on twice weekly prophylaxis was maintained over consecutive 6-month treatment periods.

CONCLUSION

- BAX 855 was efficacious for long-term prophylaxis in 234 children, adolescent, and adult PTPs with severe hemophilia A.
- The current, albeit limited experience with Q5d and Q7d prophylaxis with BAX 855 suggests that selected patients who have low ABRs on twice weekly prophylaxis may benefit from prophylaxis with prolonged infusion intervals.

ACKNOWLEDGEMENTS AND DISCLOSURES

The authors recognize with gratitude the investigators and patients who participated in the studies. The studies were sponsored by Baxalta US, Inc. and Baxalta Innovations GmbH; Baxalta, now part of Shire.
If you have any additional questions, please feel free to contact our Medical Information at medinfo@baxalta.com.

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DOI: 10.3252/pso.WFH2016.2016