Safety and Efficacy of a Pegylated Full-Length Recombinant Factor VIII With Extended Half-Life in Previously Treated Children With Hemophilia A

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INTRODUCTION

- Prophylactic infusions of factor VIII (FVIII) replacement, administered every other day or 3 times/week have been shown to be the optimal treatment to prevent or reduce bleeding in hemophilia A patients without inhibitors.[1-5]
- BAX 855, ADYNOVATE, a full-length recombinant FVIII (rFVIII) built on the plasma/albumin-free manufacturing platform of rAHF-PFM (ADVATE), covalently bound to a branched 20 kDa polyethylene glycol (PEG), was developed to extend FVIII half-life ($T_{1/2}$) thereby reducing prophylactic infusion frequency[6] or maintaining higher FVIII trough levels.
- A first-in-human study demonstrated that $T_{1/2}$ of FVIII in the circulation is prolonged by up to 1.5 times with BAX 855 compared to ADVATE. [7] Twice weekly prophylaxis with BAX 855 resulted in a significant reduction in bleeding compared to on-demand treatment in adolescent and adult previously treated patients (PTPs) with severe hemophilia A. Forty-percent of compliant subjects experienced no bleeding episodes while on study. Safety and efficacy of BAX 855 in bleed treatment were also established in this patient population. [7]
- Children are expected to specifically benefit from extended half-life FVIII concentrates that maintain hemostatic efficacy while reducing prophylactic infusion frequency and thus may help to prevent hemophilic arthropathy and disability while maintaining or improving quality of life.[3, 4, 8-10]

OBJECTIVE

- Evaluation of immunogenicity, efficacy and safety of prophylaxis with BAX 855 in previously treated patients (PTPs) < 12 years of age with severe hemophilia A.
- Evaluation of the pharmacokinetic (PK) profile of BAX 855 compared to ADVATE in a subset of subjects.

METHODS

- In this global, open-label, phase 3 study, children < 12 years of age received twice-weekly prophylaxis with BAX 855 (50 ± 10 IU/kg) for ≥ 6 months or 50 exposure days (EDs), whichever occurred last.
- Key eligibility criteria included:
  - age < 12 years
  - diagnosis of severe hemophilia A (FVIII activity <1%)
  - previous FVIII exposure ≥ 50 days for children < 6 years and ≥ 150 days for children 6 to < 12 years of age
  - no history of or currently detectable FVIII inhibitory antibodies (≥ 0.6 Bethesda units [BU] using the Nijmegen modification of the Bethesda assay)
  - no known hypersensitivity towards mouse or hamster proteins, PEG, or Tween 80
- The primary outcome measure was the development of FVIII inhibitors. Annualized bleeding rates (ABRs) were analyzed in a generalized linear model, assuming a negative binomial distribution and accounting for target joints, age, and duration of treatment.
- PK parameters were determined by a non-linear modeling population PK approach. In addition, a non-compartmental approach was extended to sparse sampling.[11; 12] These models allowed for a reduced sampling schedule in children of 3 post-infusion blood draws during a 96-hour period.

REFERENCES

1. MASAC Recommendation Concerning Prophylaxis (Prophylactic Administration of Clotting Factor Concentrate to Prevent Bleeding). 3-8-2007. National Hemophilia Foundation.
2. MASAC Recommendation Concerning Prophylaxis (Regular Administration of Clotting Factor Concentrate to Prevent Bleeding). 11-4-2007. National Hemophilia Foundation.
3. Löfqvist T, Nilsson IM, Berntorp E, Pettersson H. Haemophilia prophylaxis in young patients - a long-term follow-up. *J.Intern.Med.* 1997;241:395-400.
4. Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N.Engl.J.Med.* 2007;357:535-544.
5. Valentino LA, Mamonov V, Hellmann A, et al. A randomized comparison of two prophylaxis regimens and a paired comparison of on-demand and prophylaxis treatments in hemophilia A management. *J.Thromb.Haemost.* 2012;10:359-367.
6. Turecek PL, Bossard MJ, Graninger M, et al. BAX 855, a PEGylated rFVIII product with prolonged half-life. Development, functional and structural characterisation. *Hamostaseologie.* 2012;32 Suppl 1:S29-S38.
7. Konkle BA, Stasyshyn O, Chowdary P, et al. Pegylated, full-length, recombinant factor VIII for prophylactic and on-demand treatment of severe hemophilia A. *Blood.* 2015;126:1078-1085.
8. Roosendaal G, Lafeber F. Prophylactic treatment for prevention of joint disease in hemophilia--cost versus benefit. *N.Engl.J.Med.* 2007;357:603-605.
9. Royal S, Schramm W, Berntorp E et al. Quality-of-life differences between prophylactic and on-demand factor replacement therapy in European haemophilia patients. *Haemophilia.* 2002;8:44-50.
10. Unim B, Veneziano MA, Boccia A, Ricciardi W, Ia Torre G. Haemophilia A: Pharmacoeconomic review of prophylaxis treatment versus on-demand. *ScientificWorldJournal.* 2015;2015:596164.
11. Jaki T, Wolfsegger MJ. Estimation of pharmacokinetic parameters. *Pharm.Stat.* 2011;10:284-288.
12. Jaki T, Wolfsegger MJ. Non-compartmental estimation of pharmacokinetic parameters for flexible sampling designs. *Stat.Med.* 2012;31:1059-1073.

RESULTS

Subject Disposition

Figure 1: Flow Chart

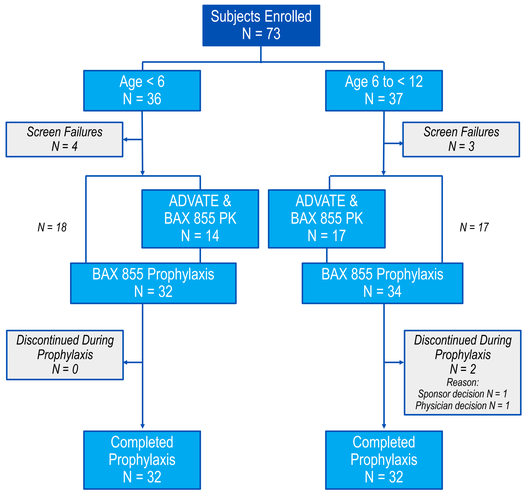


Table 1: Baseline Characteristics

Parameter	Statistics	Age < 6 (N = 32)	Age 6 to < 12 (N = 34)	Total (N = 66)
Age (years)	Median (min, max)	4.0 (1, 5)	8.0 (6, 11)	6.0 (1, 11)
Sex	Male, n (%)	32 (100.0)	33 (97.1)	65 (98.5)
	Female, n (%)	0 (0.0)	1 (2.9)	1 (1.5)
Race	Asian, n (%)	10 (31.3)	7 (20.6)	17 (25.8)
	Black or African American, n (%)	2 (6.3)	2 (5.9)	4 (6.1)
	White, n (%)	18 (56.3)	25 (73.5)	43 (65.2)
	Other, multiple n (%)	2(6.3)	0 (0.0)	2 (3.0)
Prior Treatment	Prophylactic, n (%)	32 (100.0)	29 (85.3)	61 (92.4)
	On Demand, n (%)	0 (0.0)	5 (14.7)	5 (7.6)
Number of Target Joints at Screening	0, n (%)	29 (90.6)	23 (67.6)	52 (78.8)
	1, n (%)	3 (9.4)	3 (8.8)	6 (9.1)
	2, n (%)	0 (0.0)	7 (20.6)	7 (10.6)
	3, n (%)	0 (0.0)	1 (2.9)	1 (1.5)
Hemophilic Arthropathy	Presence, n (%)	0 (0.0)	3 (8.8)	3 (4.5)
	Absence, n (%)	32 (100.0)	31 (91.2)	63 (95.5)

% = percentage of subjects in each category relative to the number of subjects in the relevant analysis set; n = number of subjects in each category; N = total number of subjects in the relevant analysis set

Immunogenicity

- The proportion of subjects with an inhibitory antibody titer ≥ 0.6 BU (using the Nijmegen modification of the Bethesda assay) after at least 50 EDs to treatment with BAX 855 was 0 (95% CI: 0.0000-0.0627, n = 57).
- There was no indication of persistent binding antibodies against FVIII, PEG-FVIII or PEG impacting PK, safety or hemostatic efficacy.
- No subject developed antibodies to host cell (Chinese hamster ovary) proteins.

Adverse Events

- The mean (± SD) number of EDs to BAX 855 was 54.0 (± 7.7) per subject.
- Overall, 4,467,796 IU of BAX 855 were infused.
- 156 AEs in 43 (65.2%) subjects were reported during the study.
- 23 (34.8%) subjects did not experience AEs.
- No AEs led to discontinuation of treatment.
- Four unrelated AEs in 3 subjects were serious including febrile neutropenia, pancytopenia, acute gastritis, and abdominal pain.
- There were no (serious) adverse drug reactions.

Prophylaxis of Bleeding

- Subjects received a median (Q1; Q3) dose of 51.3 (47.4, 53. 6) IU/kg of BAX 855 per prophylactic infusion at a median (Q1; Q3) frequency of 1.9 (1.8, 1.9) infusions per week.
- 38% (25/66) of subjects experienced no bleeding events.
- 73% (48/66) of subjects experienced no hemarthroses.
- 67% (44/66) of subjects experienced no spontaneous bleeding events.
- 91% (60/66) of subjects did not require dose adjustments during the study. Reported reasons for dose adjustment included FVIII trough levels < 1%, increased risk of bleeding, and bleeding episodes.
- The mean (± SD) interval between bleeding episodes was 2.4 (± 2.5) months.

Table 2: Annualized Bleeding Rates

ABR per Subject	Statistical Unit	Age < 6 (N = 32)	Age 6 to <12 (N = 34)	Total (N = 66)
Total	Point Estimate for Mean	2.4	3.8	3.0
	95% CI for the Mean	1.5 - 3.8	2.4 - 5.8	2.2 - 4.2
	Median	2.0	2.0	2.0
	Q1, Q3	0.0, 3.9	0.0, 5.9	0.0, 3.9
Spontaneous Bleeds	Point Estimate for Mean	1.0	1.3	1.2
	95% CI for the Mean	0.5 - 2.0	0.7 - 2.4	0.7 - 1.8
	Median	0	0	0
	Q1, Q3	0, 1.9	0, 1.9	0, 1.9
Joint Bleeds	Point Estimate for Mean	0.9	1.4	1.1
	95% CI for the Mean	0.4 - 1.9	0.6 - 2.8	0.6 - 1.9
	Median	0	0	0
	Q1, Q3	0, 0	0, 1.9	0, 1.9

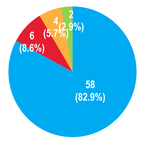
ABR = annualized bleeding rate; CI = confidence interval; Q1 = first quartile; Q3 = third quartile; N = number of subjects in the relevant analysis set.
Point estimate and 95% CIs obtained from a generalized linear model assuming a negative binomial distribution with logarithmic link function. The model includes the presence or absence of target joints and age category (< 6 versus ≥ 6 to < 12) as covariates and the duration of the observation period as an offset.

Treatment of Bleeding

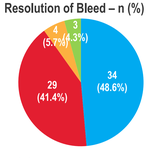
A total of 70 mild and moderate bleeding episodes in 34 subjects were treated with BAX 855. The majority (91.4%, 64/70) of bleeds was treated with 1 or 2 infusions at a mean (±SD) dose per infusion of 43.2 (±13.9) IU/kg, and in 90% (63/70), efficacy of bleed treatment was rated "excellent" or "good"

Figure 2: Characteristics of Treated Bleeding Episodes

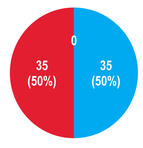
Number of Infusions to Treat Bleeding Episodes – n (%)



Hemostatic Efficacy Rating (by Patients/Parents) at Resolution of Bleed – n (%)



Severity of Bleeding Episodes– n (%)



% = percentage of bleeds in each category relative to the number of bleeds; n = number of bleeds

BAX 855 vs. ADVATE Pharmacokinetics

- BAX 855, ADYNOVATE, demonstrated an extended PK profile compared to ADVATE at the same (60 ± 5 IU/kg) dose level. Depending on the PK model and the FVIII assay used (one-stage clotting or chromogenic substrate), increases in $T_{1/2}$ and MRT with BAX 855 were 1.3 to 1.5-fold compared to ADVATE. Fold increases in the pediatric population were similar to fold increases in adults.[7]

Table 3: PK Parameter Ratios Between BAX 855 and ADVATE

Parameter	One-stage Clotting Assay N = 31	Chromogenic Substrate Assay N = 31
Non-compartmental Approach for Flexible Sampling Designs		
	Estimate	Estimate
$T_{1/2}$ (h)	1.5	1.4
MRT (h)	1.5	1.4
CL (dL/h/kg)	0.57	0.51
Non-linear Mixed Effects Model Approach (Population PK)		
	Mean	Mean
$T_{1/2}$ (h)	1.3	1.5
MRT (h)	1.3	1.5
CL (dL/h/kg)	0.76	070

CL = clearance; MRT= mean residence time; N = number of subjects; $T_{1/2}$ = terminal half-life

Summary

- BAX 855 is an extended half-life, pegylated full-length rFVIII built on ADVATE.
- Efficacy, safety, immunogenicity and PK of BAX 855 were evaluated in pediatric PTPs < 12 years of age. Subjects received twice-weekly infusions of 50 ± 10 IU/kg BAX 855 for ~6 months (≥ 50 EDs).

Safety

- No subject developed inhibitory antibodies to FVIII.
- No subject developed persistent binding antibodies to FVIII, PEG-FVIII or PEG impacting PK, safety or hemostatic efficacy.
- No product-related AEs or SAEs were reported.
- No subject discontinued treatment due to AEs.

Efficacy – Prevention of Bleeding

- 38% of subjects did not experience any bleeds and 73% of subjects did not experience any joint bleeds.
- Point estimates were 3.0 (median 2.0) for the mean total ABR and 1.1 (median 0) for the mean joint ABR.

Efficacy – Treatment of Bleeding

- All bleeding episodes were minor or moderate.
- 91% of treated bleeding events were treated with 1 or 2 infusions.
- 90% of bleeding events received treatment ratings of "excellent" or "good".

Pharmacokinetics

- Increases in $T_{1/2}$ and MRT with BAX 855 were 1.3 to 1.5-fold compared to ADVATE.
- Fold increases in $T_{1/2}$ and MRT in the pediatric population were similar to fold increases in adults. [7]

CONCLUSION

- BAX 855 was shown to be safe and efficacious for twice-weekly prophylaxis and the control of bleeding in children with hemophilia A.

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