Poster #166

Impact of maintaining higher FVIII trough levels with BAX 855: Rationale and design of the PROPEL Study

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INTRODUCTION

- BAX 855 (ADYNOVATE) is a polyethylene glycol (PEG)ylated, full-length, recombinant factor VIII (FVIII) built on the protein ADVATE
- In the BAX 855 Pivotal study, 39.6% of patients achieved zero bleeds and 57.4% experienced zero joint bleeds while on prophylaxis (per protocol analysis set).[1] In the BAX 855 Pediatric study, 37.9% of patients achieved zero bleeds and 72.7% experienced zero joint bleeds.[2] In both studies, the FVIII replacement regimens were selected to ensure that most patients maintained ≥ 1% FVIII levels, in accordance with current guidelines.[3]
- However, a 1% FVIII trough is not enough for all patients to completely eliminate bleeding episodes. In particular, patients with preexisting joint disease or active lifestyles are more likely to bleed, therefore requiring higher trough levels.
- Broderick et al. demonstrated that the bleeding incidence associated with physical activity was lowered by 2% for every 1% increase in clotting factor level.[4]
- Den Uijl, et al. reported that the number of joint bleeds is close to zero in patients with hemophilia A who have baseline FVIII levels above 12%.[5]
- The goal of prophylaxis is to enable more patients to achieve zero bleeds and preserve long-term joint health and quality of life.

OBJECTIVE

- To determine if targeting higher trough levels during BAX 855 prophylaxis further reduces bleeding episodes and enables more patients to achieve zero bleeds.

METHODS

BAX 855 Clinical Studies Included in the Integrated Summary of Efficacy (as of February 2016)

PIVOTAL STUDY (NCT01736475)
- Age 12-65 years
- Prophylaxis: 45 ± 5 IU/kg twice weekly for ≥50 EDs or 6 months
- On-demand (N=17): 10 to 60 ± 5 IU/kg

Complete

PEDIATRIC STUDY (NCT02210091)
- Age <12 years
- Prophylaxis:50 ± 10 IU/kg twice weekly for ≥50 EDs or 6 months

Complete

SURGERY STUDY (NCT01913405)

Ongoing

CONTINUATION STUDY (NCT01945593)
- Age ≤75 years

Dosing regimen options

Prophylaxis, twice weekly
- Age ≥12 years: 45 ± 5 IU/kg
- Age <12 years: 50 ± 10 IU/kg

PK-tailored prophylaxis
- Targeting FVIII trough levels ≥3%
- 25-80 IU/kg at least once weekly

Extended interval dosing
- Prophylaxis Q5d (30-80 IU/kg) if spontaneous ABR (sABR)=0 for prior 6 months on twice weekly prophylaxis
- Prophylaxis Q7d (45 ± 5 IU/kg) if sABR=0 for prior 6 months on Q5d prophylaxis

Ongoing

- Annualized bleeding rate (ABR) outcomes were compared for the Pharmacokinetic (PK)-tailored prophylaxis group (from the Integrated Summary of Efficacy, ISE) with those of the prophylaxis groups in the Pivotal and Pediatric studies receiving a fixed dose twice weekly prophylactic regimen.
- The ISE was conducted to evaluate the hemostatic efficacy of long-term prophylaxis in the BAX 855 clinical program.[6]

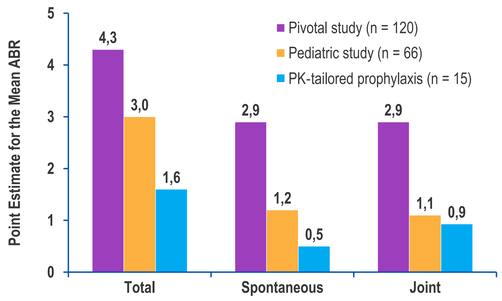
RESULTS

Table 1: Subject Demographics

Age Range	Pivotal Study	Pediatric Study	PK-tailored Prophylaxis
<12 years	0	66	6
12 to <18 years	23	0	3
≥ 18 years	97	0	6
Total	**120**	**66**	**15**

- Of the 15 patients included in the PK-tailored prophylaxis group for at least 6 months, 6 had transitioned from the Pediatric Study, and 9 from the Pivotal study.
- ISE data were based on the Full Analysis Set (FAS), so the FAS from the Pivotal and Pediatric studies were also utilized in this analysis.
  - The ISE twice weekly prophylaxis group was *not* included because patients with zero bleeds were eligible to switch to Q5d or Q7d dosing, thereby shifting the mean ABR of this group slightly higher.
- In the ISE, ABRs were evaluated by point estimates for the mean (95% CI) using a negative binomial model analysis, accounting for target joints, age, and duration of treatment.
  - The same model was used for the ABRs reported here from the Pivotal and Pediatric studies.

Figure 1: ABR of PK-tailored Prophylaxis (Targeting ≥ 3% FVIII Trough) and Fixed Twice Weekly Prophylaxis (Targeting ≥ 1% FVIII Trough)



Lower ABR During PK-tailored Prophylaxis (≥ 3% FVIII Trough Levels)

- These preliminary data suggest that targeting higher FVIII trough levels (≥ 3%) with FVIII replacement results in lower ABRs than does the current standard (~1%).
- As previously reported, patients receiving twice weekly prophylaxis in the Pivotal study had median total, spontaneous, and joint ABRs of 1.9, 0.0, and 0.0, with similar median ABRs from the Pediatric study.[1,2]
- The lower ABR values seen in the Pediatric study compared to the Pivotal study is most likely due to the lower percentage of patients in the Pediatric study with one or more target joints at screening compared to patients in the Pivotal study (65.0%).

PROPEL

PROspective, randomized, multi-center clinical study comparing the safety and efficacy of BAX 855 following

PK-guided prophylaxis targeting two different Factor

Eight (FVIII) trough

Levels in subjects with severe Hemophilia A

PROPEL Study

- To further investigate the clinical benefit of maintaining higher FVIII trough levels with factor replacement, a controlled study was initiated: BAX 855 PK-Guided Dosing Study (NCT02585960), or "PROPEL."
- BAX 855 infusions are either twice weekly (targeting 1-3% FVIII trough) or every other day (targeting 8-12% FVIII trough). The dose depends on the patient's individual PK.

Main Eligibility Criteria
- Severe hemophilia A (FVIII < 1%)
- Age 12-65 years
- Previously treated patient, receiving either on-demand or prophylactic treatment
- Annual bleeding rate of ≥ 2, documented and treated during the past 12 months
- No presence or history of FVIII inhibitor (≥ 0.6 BU; Nijmegen modification of Bethesda assay)

Individual PK Assessment → Randomize

FVIII Trough Level: 1–3%
Twice weekly BAX 855 prophylaxis
N = 48

6 months: Run-in / dose adjustment → 6 months: Evaluation of primary endpoint

FVIII Trough Level: approx. 10% (8–12%)
Every other day BAX 855 prophylaxis
N = 48

Primary Objective

- Compare proportion of subjects in each group (1-3% vs. 8–12% trough level) achieving a total ABR of 0 in the second 6-month study period

Secondary Objectives (compared for each treatment arm)

EFFICACY	• Proportion of subjects with total, spontaneous, and joint ABR of 0 during the second 6-month study period • Proportion of subjects with total, spontaneous, and joint ABR of < 2 throughout the study • Total, spontaneous, and trauma-related ABRs • ABR on study vs. historical ABR • BAX 855 weight-adjusted consumption • Joint status using the Hemophilia Joint Health Score • Health-related quality of life (HRQoL) & pharmacoeconomic outcomes • Hemostatic efficacy in the control of bleeding episodes
SAFETY	• Adverse events • Immunogenicity
PK	• PK parameters at baseline and steady state
PATIENT REPORTED OUTCOMES	• HRQoL (SF-36, EQ-5D) • Change in bleed and pain severity scores (Haemo-SYM) • Change in physical activity participation from baseline to follow-up
EXPLORATORY	• Correlation of thrombin generation assay with FVIII levels and ABR • Biomarkers

Currently recruiting

- North America, Europe, Asia Pacific and Israel.

Assumptions

- By increasing the target FVIII trough level with FVIII replacement from 1–3% to 8–12%, the proportion of bleed-free patients is anticipated to increase from approximately 40% (as seen in the Pivotal Study) to approximately 70%.
- These estimates are from simulations based on the ADVATE Prophylaxis study and the BAX 855 Pivotal study.[1,7]

DISCUSSION

- Preliminary results from the BAX 855 ISE suggest that lower ABRs may be achieved when targeting higher FVIII trough levels (≥ 3% compared to 1%) with FVIII replacement.
- The novel PROPEL study further evaluates the benefits of maintaining higher FVIII trough levels, and if they can allow a greater proportion of hemophilia A patients with hemophilia A to achieve zero bleeds.
- Considering that even a single severe bleed can cause irreversible damage, the results will provide additional clinical knowledge to improve outcomes, especially for patients who require higher FVIII trough levels.

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DISCLOSURES

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