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

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INTRODUCTION

- BAX 855 (ADVATE) is a polyethylene glycol (PEG)ylated, full-length recombinant factor VIII (FVIII) built on the protein ADVATE.
- In the BAX 855 Pivotal study, 38.9% of patients achieved zero bleeds and 77.4% experienced zero joint bleeds while on prophylaxis (per protocol analysis set). In the BAX 855 Pediatric study, 37.9% of patients achieved zero bleeds and 72.2% experienced zero joint bleeds. In both studies, the FVIII replacement regimens were selected to ensure that most patients maintained ≥ 2 FVIII levels, in accordance with current guidelines.
- However, a 1% FVIII trough is not enough for all patients to completely eliminate bleeding episodes. In particular, patients with presenting joint disease or active lifestyles are more likely to bleed, thereby requiring higher trough levels.
- Brodie et al. demonstrated that the bleeding incidence associated with physical activity was lowered by 2% every 1% increase in clotting factor level.1

OBJECTIVE

- To determine if targeted 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 (NCT01783471)
- Age 12-65 years
- Prophylaxis: 41.3 ± 12.6 kg/m² twice weekly or 90 IU/kg every 2 weeks
- On-treatment (HOA): 33.8 ± 12.6 kg/m²

STUDY (NCT01913405)
- Age 6-12 years
- Prophylaxis: 36.5 ± 13.0 kg/m² twice weekly or 92 IU/kg every 2 weeks

PBCT STUDY (NCT02200581)
- Age 6-12 years
- Prophylaxis: 36.5 ± 13.0 kg/m² twice weekly or 92 IU/kg every 2 weeks

CONTINUATION STUDY (NCT01948599)
- Age ≥12 years
- Dosing regimen unchanged

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- 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), as the FAS from the Pivotal and Pediatric studies were also utilized in this analysis.
- The ISE twice-weekly prophylaxis group was age-matched because patients with zero bleeds were selected to target 50 IU/kg/day, 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 ARBs reported here from the Pivotal and Pediatric studies.

RESULTS

- Lower ABR During PK-tailored Prophylaxis (≥ 3% FVIII Trough Level)
  - These preliminary data suggest that targeting higher FVIII trough levels (≥ 3%) with FVIII replacement results in lower ABRs than those currently used (standard care).
  - As previously reported, patients receiving twice-weekly prophylaxis in the Pivotal study had median total, spontaneous, and joint ABRs of 1.3, 0.3, and 0.3, with similar median ABRs from the Pediatric study.1
  - 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 major joints at screening compared to patients in the Pivotal study (60%).

Figure 1: ABR of PK-tailored Prophylaxis (Targeting ≥ 3% FVIII Trough) and Fixed Twice Weekly Prophylaxis (Targeting ≥ 2% FVIII Trough)

PROPEL Study

- To further investigate the clinical benefit of maintaining higher FVIII trough levels with long-term prophylaxis, a controlled study was initiated in the BAX 855 Pivotal Study (NCT02589661) and PROPEL PROspective, randomized, multi-center clinical study comparing the safety and efficacy of BAX 855 following PK-guided prophylaxis targeting two different FVIII levels in subjects with severe Hemophilia A

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REFERENCES