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

Brigit Abbbeuhl,1 Werner Engl,1 Lisa Patrone,2 and Anne Prener3

1Shire, Vienna, Austria; 2Shire, Westlake Village, CA; 3Shire, Cambridge, MA

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.
- BAX 855, a pegylated glycoprotein, full-length recombinant FVIII (rFVIII), is built on the plasma-safe, human manufacturing platform of rFVIII-hFVIII (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 up to 1.5 times compared to ADVATE and that single infusions were well tolerated.2
- 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.6
- The BAX 855 surgery study demonstrated the safety and efficacy of BAX 855 for perioperative management.7
- 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 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

<table>
<thead>
<tr>
<th>Study Status</th>
<th>Description</th>
<th>ClinicalTrials.gov</th>
<th>N (n): Number of patients treated in the study (number of patients unique to that study)</th>
<th>Treatment Duration</th>
<th>Study Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pivotal</td>
<td>Phase 3, perioperative</td>
<td>EudraCT: 0000742  1*  NCT01945593  2*</td>
<td>137 (20)</td>
<td>6 months</td>
<td>Adolescents (≥ 18 years)</td>
</tr>
<tr>
<td>Surgery</td>
<td>Phase 3, perioperative</td>
<td>EudraCT: 0000742  1*  NCT01945593  2*</td>
<td>174 (0)</td>
<td>6 months</td>
<td>Adults (≥ 18 years)</td>
</tr>
<tr>
<td>Pediatric</td>
<td>Phase 3, long-term</td>
<td>NCT01945593  1*  NCT0375047  2*</td>
<td>51.2 ± 5.1%</td>
<td>2 years</td>
<td>Children (≥ 6 years)</td>
</tr>
<tr>
<td>Pediatric</td>
<td>Phase 3, short-term</td>
<td>NCT0375047  2*</td>
<td>51.2 ± 5.1%</td>
<td>6 months</td>
<td>Children (≥ 6 years)</td>
</tr>
</tbody>
</table>

RESULTS

- In a protocol amendment, these treatment options were revised to twice weekly BAX 855 for adolescents and adults ≥ 12 years and 50 ± 10 IU/kg for children < 12 years prophylaxis or for bleeds prophylaxis targeting 2–3 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 (SD) 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).

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

<table>
<thead>
<tr>
<th>All Ages</th>
<th>Younger Children (≤ 6 years)</th>
<th>Older Children (≥ 6 to &lt; 18 years)</th>
<th>Adolescents (≥ 18 years)</th>
<th>Adults (≥ 18 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.8 ± 5.8</td>
<td>6.0 ± 5.0</td>
<td>5.9 ± 5.7</td>
<td>6.1 ± 5.5</td>
<td>6.2 ± 5.6</td>
</tr>
</tbody>
</table>

In order to ensure that the overall treatment is interpreted correctly, this means that the ABRs are not adjusted for any covariates, except for the treatment regimen. This is because the treatment regimen is a fixed effect and not a random effect in the model. In other words, the treatment regimen is not left to chance and is not included as a random effect in the model. Therefore, the ABRs for all ages are not adjusted for any covariates, including the treatment regimen.

- For BAX 855 patients on weekly prophylaxis (included 66 children, 24 adolescents, and 123 adults), joint episodes for teens (median and interquartile range [IQR]: 2.0 [1.0–3.0] for FVIII levels) were reduced to 0.7 for 1.24 (1.0–1.62) for spontaneous bleeding. This means that the number of joint episodes was reduced from 2.0 to 0.7 for adolescent and adult patients and from 1.24 to 1.0 for spontaneous bleeding.

REFERENCES


ACKNOWLEDGEMENTS AND DISCLOSURES

The lead authors will be available for all questions and are not paid to participate in this study. The authors are employees of Baxalta US, Inc. and Shire, Cambridge, MA. For all preliminary versions, please view them to Shire Bavarianhaemophilia.com. Author(s) are employees of Baxalta US, Inc. and Shire, Cambridge, MA.