Factor VIII use in the treatment of breakthrough bleeds in hemophilia A patients without inhibitors on emicizumab prophylaxis: the phase III HAVEN 3 study experience

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INTRODUCTION

Emicizumab – a bispecific antibody – binds activated factor IX (FIXa) and FX to restore the hemostatic function of missing FVIIIa in persons with hemophilia A (pHA).

HAVEN 3 (NCT02482637), a phase III study in adolescent/adult pHA without inhibitors, demonstrated the efficacy and safety of emicizumab prophylaxis once every week (QW) or once every 2 weeks (Q2W) vs. no prophylaxis.

• A 65% decrease in bleeding was observed with emicizumab prophylaxis over previous FIX prophylaxis (1.38 vs 5.6 bleeds/yr).

• Emicizumab prophylaxis in non-inferior study (NIS) prior to enrollment in HAVEN 3.

• On-demand emicizumab was prescribed at the investigator’s discretion in the NIS and in HAVEN 3. In HAVEN 3, investigators were advised to treat breakthrough bleeds (BTBs) with the lowest FVIII dose expected to achieve hemostasis.

• To characterize the dose and frequency of replacement FVIII used for the treatment of BTBs in the 48 pHA previously enrolled in the NIS who were subsequently treated with emicizumab during HAVEN 3.

METHODS

• In HAVEN 3 (Figure 1), eligible participants were aged ≥12 years with severe congenital hemophilia A, without current FVIII inhibitors (<6 Bethesda units/ml), who were managed on episodic or prophylactic FVIII.

Figure 1. HAVEN 3 study design.1 These analyses focus on patients from Arm D who received prior FVIII prophylaxis as part of the NIS.

RESULTS

• Of 48 participants receiving FVIII prophylaxis in the NIS, 29 (60-4%) experienced a total of 137 treated bleeds. While receiving emicizumab prophylaxis during HAVEN 3, 27 of the same 48 participants (56.3%) experienced 71 treated bleeds (Table 1).

• Both the annualized infusion rate and the cumulative dose of on-demand FVIII per participant were higher while receiving FVIII prophylaxis during the NIS than when receiving emicizumab prophylaxis during HAVEN 3 (Table 1).

• At the individual bleed level, the number of on-demand FVIII infusions and the total cumulative FVIII dose per treated bleed indicate that participants were administered a similar amount of medication to treat bleeds during both the NIS and HAVEN 3 study periods (Table 1, Figure 2).

• Further characterization of the treated bleeds in this intra-patient analysis showed similar rates of joint bleeds and muscle bleeds between the NIS and HAVEN 3 exposure periods (57 versus 61% and 17 versus 14%, respectively).

Table 1. Analyses of treated bleeds. NIS FVIII prophylaxis versus HAVEN 3 emicizumab prophylaxis (Arm D).

<table>
<thead>
<tr>
<th>Bleed parameter</th>
<th>NIS</th>
<th>HAVEN 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total treated bleeds, n</td>
<td>137</td>
<td>71</td>
</tr>
<tr>
<td>Per-participant exposure years (median)</td>
<td>3.0 mg/kg</td>
<td>3.0 mg/kg</td>
</tr>
<tr>
<td>Total treated bleeds, n</td>
<td>71</td>
<td>71</td>
</tr>
<tr>
<td>Median cumulative dose per bleed, median (IQR) (IU/kg)</td>
<td>0.6 (0.6)</td>
<td>0.6 (0.6)</td>
</tr>
<tr>
<td>Median number of infusions per bleed, median (IQR)</td>
<td>2.0 (1.0)</td>
<td>2.0 (1.0)</td>
</tr>
</tbody>
</table>

• These analyses compare on-demand FVIII treatment for BTBs while receiving prophylactic FVIII during the NIS versus while receiving emicizumab prophylaxis during HAVEN 3 (Arm D, Intra-patient comparison).

• A bleed was defined starting from the first sign of bleeding and ending 72 hours after the last treatment for the bleed, within which any symptoms of bleeding at the same location or for which injections were ≥72 hours apart were considered the same bleed. Any injection to treat the bleed, taken ≥72 hours after the preceding injection, is considered from the first injection to treat a new bleed at the same location.

• Only on-demand FVIII use for the treatment of BTBs is included in these analyses. Any other use of FVIII (e.g., prophylactic FVIII, preventive dosing prior to activity, treatment for surgical procedures) was not included in these analyses.

• Annualized on-demand FVIII use was calculated by dividing the total days in the efficacy period and multiplying the resulting daily consumption by 365.25.

• No formal statistical inferencing (i.e. calculation of p-values) have been conducted.

CONCLUSIONS

• These analyses revealed a lower annualized infusion rate and a correspondingly lower annualized cumulative dose of on-demand FVIII treatment for BTBs with emicizumab prophylaxis in HAVEN 3 (Arm D) compared with FVIII prophylaxis in the NIS as a result of the overall reduction in bleed frequency.

• The amount of on-demand FVIII used per bleeding episode was comparable between the NIS and HAVEN 3 and similar by location of bleed.

• The treatment of individual bleeds was similar regardless of the type of prophylaxis (emicizumab versus FVIII) administered.

REFERENCES


DISCLOSURES

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