Factor VIII Inhibitor Testing Using a Validated Chromogenic Bethesda Assay in HAVEN 1 (BH29884), a Phase 3 Trial of Emicizumab in Persons with Hemophilia A with Inhibitors

Adakewicz JI,1 Schmitt C,2 Askianus E,2 Xu J,1 Levy GG,1 Kim B,1 Calatzis A2
1Genentech Inc., South San Francisco, United States; 2F. Hoffmann-La Roche Ltd, Basel, Switzerland; 3Roche Diagnostics International Ltd, Rotkreuz, Switzerland

BACKGROUND

- Emicizumab (ACE910), a novel bispecific antibody, is under investigation for prophylactic treatment of persons with hemophilia A (PwHA) (Figure 1).
- In a Phase 3 trial of adolescent and adult PwHA ≥12 years of age with inhibitors (phase II-3 ClinicalTrials.gov NCT027022321), twice-weekly emicizumab was continued in PwHA who were not exposed previously to any FVIII or FIXa inhibitor. All samples were compared with non-inhibitor and compared with prior prophylactic bypassing agent regimens (Oldenburg et al. 2017; Abstract AS01.1).

OBJECTIVES

- To validate the CBA for use in the presence of emicizumab.
- To measure FVIII inhibitor titers and assess change over time for PwHA with inhibitors enrolled in the HAVEN 1 Phase 3 trial (Study BH29884; ClinicalTrials.gov NCT02622321).

METHODS

- The CBA was implemented according to the methodology of Miller et al.1
- Factor VIII (FVIII) inhibitors in PwHA are commonly measured using a mixing-coiling method (Bethesda assay), in which residual FVIII activity is quantified by a one-stage FVIII assay (Figure 2).
- Emicizumab is not inactivated by heat treatment nor by FVIII inhibitors, and therefore interferes with standard Bethesda assays, leading to false-negative results.
- The Chromogenic Bethesda assay (CBA) uses a chromogenic FVIII activity assay containing bovine components that are insensitive to emicizumab, allowing detection and quantification of FVIII inhibitors in FVIII-depleted emicizumab (Figure 2).

RESULTS

- Inhibitor titers in Chromogenic Bethesda Units (CBU) were calculated based on results from all patients who received at least one dose of emicizumab prophylaxis in HAVEN 1 (Figure 4).

CONCLUSIONS

- The Chromogenic Bethesda Assay is a robust method for determining FVIII inhibitor titers and is accurate in the presence of emicizumab.
- FVIII inhibitor titers were measured successfully in HAVEN 1 for PwHA with inhibitors receiving prophylaxis with emicizumab.
- A slight trend toward lower median FVIII inhibitor titers were observed, which likely resulted from effective treatment with emicizumab.

ACKNOWLEDGMENTS AND DISCLOSURES

- This work was sponsored by F. Hoffmann-La Roche Ltd
- This work was sponsored/supported by Roche at this congress

REFERENCES