Identifying Efficacious Thresholds for Bleeding Risk Reduction in Relation to Factor IX (FIX) Levels in Hemophilia B Patients Receiving IDELVION

C Fosser¹, J Roberts², M Tortorici², I Jacobs², J Sidhu²
¹Cytel, Cambridge, MA; ²CSL Behring, King of Prussia, PA

FIX replacement is effective therapy for hemophilia B patients, as a rationale for keeping higher trough levels of FIX so that patients with severe hemophilia (FIX <1%) transition to moderate (FIX of 1-5%) or mild disease states (FIX >5%) exists. An analysis was done to robustly define the FIX exposure versus outcome relationship.

A Cox proportional hazards model related time-to-bleed data from pooled adult data from the IDELVION Phase 3 program and measures of exposure (FIX activity) and dosing regimen, and also tested the influence of baseline FIX. FIX levels were simulated using a PopPK model. The analysis included all bleeding episodes in patients treated with prophylaxis and/or on-demand regimens. Regimens included 50 IU/kg (every 1 week) and 75 IU/kg (every 2 weeks, or every 10 days). 478 bleeding episodes from 57 adult patients were included in the analysis.

Patients maintaining cumulative FIX activity trough levels above 5% and 10% were predicted to have significant reductions in bleeding risk of 83% and 81%, respectively, per 1 year above this level. Furthermore, a direct evaluation relating daily FIX trough activity to daily bleeding risk found that >2%, >5% and >10% FIX activity thresholds were significant predictors of bleeding events with 69% (53% to 80%), 77% (67% to 84%), and 78% (69% to 85%) risk reductions (95% CI), respectively.

This exposure-response analysis of IDELVION determined a strong relationship between FIX activity and bleeding risk reduction. Trough FIX activity above 5% (either cumulatively or directly) was identified as a statistically significant and sufficient threshold for reduction of bleeding risk in adult hemophilia B patients receiving IDELVION. Trough FIX activity > 10% was also predictive of significant risk reduction, and the magnitude of risk reduction was similar to that of achieving levels > 5%. This analysis supports the quantitative rationale for optimization of IDELVION regimens by keeping FIX activity trough levels above 5% to 10%.