

Concizumab: a novel anti-TFPI therapeutic for hemophilia

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Abstract

Concizumab is a novel subcutaneous prophylactic therapy for hemophilia. It is a hemostatic rebalancing agent that binds to the Kunitz-2 domain of tissue factor pathway inhibitor (TFPI), one of the molecules that contributes to downregulation of coagulation thereby preventing TFPI from binding to and blocking the factor Xa (FXa) active site. When the TFPI inhibitory activity is decreased, sufficient FXa is produced by the FVIIa-tissue factor complex to achieve hemostasis. On the basis of this mechanism of action, concizumab is expected to be equally effective in hemophilia A and B, regardless of inhibitor status. Moreover, the concizumab mechanism of action does not interfere with the regulation of coagulation downstream of TFPI. Results from 2 phase 2 trials in patients with hemophilia A or B with and without inhibitors demonstrated that concizumab had a favorable safety profile, with no deaths, no thromboembolic events, and no adverse events leading to withdrawal. Clinical proof of concept in prevention of bleeding episodes was confirmed in both concizumab phase 2 trials across all hemophilia subtypes assessed, with a statistically significant and clinically relevant reduction in annualized bleeding rates observed in inhibitor patients compared to those who received on-demand treatment. On the basis of phase 2 results, the US Food and Drug Administration granted concizumab Breakthrough Therapy designation for hemophilia B with inhibitor patients, a rare and vulnerable patient subgroup that currently has the highest unmet medical need. In the ongoing concizumab phase 3 trials, an optimized dosing regimen will be administered in patients with hemophilia A or B with and without inhibitors.

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Contribution: A.D.S. served as an investigator during the concizumab explorerTM4 trial, recruited patients into the study, and analyzed and interpreted the data.

Conflict-of-interest disclosure: A.D.S. has served as principal investigator for 3 Novo Nordisk-sponsored research studies.

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