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Antibody for severe hemophilia a may reduce injections needed to prevent bleeding

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An antibody engineered to prevent excessive bleeding in patients with severe hemophilia A may be safe and effective, and require fewer injections than existing options, according to a first-in-human study of the treatment published online today in *Blood*, the Journal of the American Society of Hematology (ASH).

Hemophilia A is an inherited bleeding disorder caused by a deficiency of functioning factor VIII (FVIII), a protein essential to clotting. Because their blood does not clot properly, people with hemophilia A have a high risk of excessive internal and external bleeding and may suffer complications in the joints, muscles, and organs. Half of patients with hemophilia A have the severe form of the disorder, characterized by extremely low levels of FVIII in the blood. Standard care for these patients focuses on preventing bleeding episodes by maintaining acceptable levels of FVIII, by administering either engineered or plasma-derived FVIII. While this therapy is effective, patients must self-inject FVIII product twice or three times every week intravenously, which represents a significant burden on these patients and their families. Furthermore, 20 to 30 percent of people with severe hemophilia A develop antibodies to FVIII product (termed "FVIII inhibitors").

To create a longer-lasting preventive therapy for severe hemophilia A-associated bleeding, a group of Japanese researchers launched a first-in-human Phase I trial to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of ACE910, a bispecific antibody that mimics FVIII and works with other clotting factors to make the blood clot

properly. Due to the different molecular structure from FVIII, the effect of ACE910 is not expected to be disturbed by FVIII inhibitors, and ACE910 is unlikely to induce development of FVIII inhibitors. Researchers enrolled 40 Japanese and 24 Caucasian healthy male volunteers ages 20 to 44 intending to evaluate and compare the drug's activity in these groups. In part A of the study, the Japanese volunteers were randomized to receive one of five doses of ACE910 (ranging from 0.001 to 1 mg/kg) or placebo subcutaneously. In part B, the Caucasian volunteers were randomized to receive one of three doses (ranging from 0.1 to 1 mg/kg) or placebo subcutaneously. Volunteers were monitored based on their dose group, ranging from four weeks of observation for 0.001 mg/kg to 24 weeks for 1 mg/kg.

Doses of ACE910 up to 1 mg/kg appeared to be safe, as researchers observed minimal adverse events in both the Japanese and Caucasian volunteers. Researchers did not observe any cases of hypercoagulability. All reported adverse events were not serious and did not lead to study withdrawal. Additionally, ACE910 absorbed into the plasma at a steady rate similar for both Japanese and Caucasian volunteers and remained in the blood with a half-life of four to five weeks, suggesting that the drug's therapeutic effects could be sustained with once-weekly subcutaneous dosing of ACE910.

"These data are very encouraging for patients with severe hemophilia A irrespective of the presence of FVIII inhibitors, as ACE910 has the potential to offer the opportunity to live more normal lives without constantly planning around the next injection," said study author Midori Shima, MD, PhD, of Nara Medical University. "The first clinical investigation of this drug in hemophilia A patients with or without FVIII inhibitors has already been implemented, and Phase III studies are being planned to start in the near future."