Documents

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Gene Therapy with Etranacogene Dezaparvovec for Hemophilia B

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[a] Departments of Pediatrics and Pathology, University of Michigan, Ann Arbor, MI, United States
[b] The Department of Hematology, Erasmus University Medical Center, University Medical Center Rotterdam, Rotterdam, Netherlands
[c] Van Creveldkliniek, University Medical Center Utrecht, University Utrecht, Utrecht, Netherlands
[d] Vascular Medicine, Amsterdam University Medical Center, University of Amsterdam, Netherlands
[e] Amsterdam Cardiovascular Sciences, Pulmonary Hypertension and Thrombosis, Netherlands
[f] UniQure Biopharma, Amsterdam, Netherlands
[g] University Medical Center Groningen, Groningen, Netherlands
[h] Yale University, School of Medicine, New Haven, CT, United States
[i] American Thrombosis and Hemostasis Network, Rochester, NY, United States
[j] The Department of Medicine, UNC Blood Research Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States
[k] The Center for Bleeding Disorders and Coagulation, Department of Oncology, Careggi University Hospital, Florence, Italy
[l] The Department of Hemostaseology and Hemophilia Center, Medical Clinic 2, Institute of Transfusion Medicine and Immunohematology, University Hospital Frankfurt, Frankfurt, Germany
[m] The Comprehensive Care Hemophilia Treatment Center, Vivantes Klinikum im Friedrichshain, Berlin, Germany
[n] The Department of Vascular Medicine and Hemostasis, Hemophilia Center, University Hospitals Leuven, Leuven, Belgium
[o] The Division of Hematology, Cliniques Universitaires Saint-Luc, Brussels, Belgium
[p] Université Catholique de Louvain, Louvain-la-Neuve, Belgium
[q] The Department of Hematology, Rigshopitalet Copenhagen, Copenhagen, Denmark
[r] National Coagulation Centre, St. James's Hospital, Dublin, Ireland
[s] Barts and the London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom
[t] The Royal London Hospital Haemophilia Centre, Barts Health NHS Trust, London, United Kingdom
[u] University Hospital Southampton, National Institute for Health and Care Research, Clinical Research Facility, Southampton, United Kingdom
[v] Cambridge University NHS Foundation Trust, Addenbrooks Hospital, Cambridge, United Kingdom
[w] The Department of Translational Medicine, Lund University, The Department of Hematology Oncology and Radiation Physics, Skåne University Hospital, Malmö, Sweden
[x] The Department of Pediatrics, University of Utah, Primary Children's Hospital, Salt Lake City, UT, United States
[y] University of South Florida, Tampa, FL, United States
[z] The Department of Medicine, Hemophilia and Thrombosis Treatment Center, San Diego, CA, United States
[aa] The Cancer and Blood Disorders Institute, Children's Hospital Los Angeles, United States
[ab] The Orthopaedic Hemophilia Treatment Center, The Luskin Orthopaedic Institute for Children, United States
[ac] The University of Southern California, Keck School of Medicine, Los Angeles, CA, United States
[ad] The Center for Inherited Blood Disorders, Orange, CA, United States
[ae] Arkansas Children's Hospital, Pulaski, University of Arkansas for Medical Sciences, Little Rock, United States
[af] University of Texas Health Science Center, McGovern Medical School, Gulf States Hemophilia and Thrombophilia Center, Houston, TX, United States
[ag] Washington Center for Bleeding Disorders, University of Washington, Seattle, WA, United States
[ah] Hemophilia and Thrombosis Center, University of Colorado, Anschutz Medical Campus, Aurora, CO, United States

[ai] The Department of Pathology, Microbiology and Immunology, Vanderbilt University Medical Center, Nashville, TN, United States
[aj] UniQure, Lexington, MA, United States
[ak] CSL Behring, King of Prussia, PA, United States
[al] The Institute of Experimental Hematology and Transfusion Medicine, University Hospital Bonn, Medical Faculty, University of Bonn, Bonn, Germany

Abstract
Background: Moderate-to-severe hemophilia B is treated with lifelong, continuous coagulation factor IX replacement to prevent bleeding. Gene therapy for hemophilia B aims to establish sustained factor IX activity, thereby protecting against bleeding without burdensome factor IX replacement. Methods: In this open-label, phase 3 study, after a lead-in period (≥6 months) of factor IX prophylaxis, we administered one infusion of adeno-associated virus 5 (AAV5) vector expressing the Padua factor IX variant (etranacogene dezaparvovec; 2×1013 genome copies per kilogram of body weight) to 54 men with hemophilia B (factor IX activity ≤2% of the normal value) regardless of preexisting AAV5 neutralizing antibodies. The primary end point was the annualized bleeding rate, evaluated in a noninferiority analysis comparing the rate during months 7 through 18 after etranacogene dezaparvovec treatment with the rate during the lead-in period. Noninferiority of etranacogene dezaparvovec was defined as an upper limit of the two-sided 95% Wald confidence interval of the annualized bleeding rate ratio that was less than the noninferiority margin of 1.8. Superiority, additional efficacy measures, and safety were also assessed. Results: The annualized bleeding rate decreased from 4.19 (95% confidence interval [CI], 3.22 to 5.45) during the lead-in period to 1.51 (95% CI, 0.81 to 2.82) during months 7 through 18 after treatment, for a rate ratio of 0.36 (95% Wald CI, 0.20 to 0.64; P<0.001), demonstrating noninferiority and superiority of etranacogene dezaparvovec as compared with factor IX prophylaxis. Factor IX activity had increased from baseline by a least-squares mean of 36.2 percentage points (95% CI, 31.4 to 41.0) at 6 months and 34.3 percentage points (95% CI, 29.5 to 39.1) at 18 months after treatment, and usage of factor IX concentrate decreased by a mean of 248,825 IU per year per participant in the post-treatment period (P<0.001 for all three comparisons). Benefits and safety were observed in participants with predose AAV5 neutralizing antibody titers of less than 700. No treatment-related serious adverse events occurred. Conclusions: Etranacogene dezaparvovec gene therapy was superior to prophylactic factor IX with respect to the annualized bleeding rate, and it had a favorable safety profile. © 2023 Massachusetts Medical Society.

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Correspondence Address
Pipe S.W.; Departments of Pediatrics and Pathology, 1500 E. Medical Center Dr., United States; email: ummdswp@med.umich.edu

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