Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Peyvandi F, Mannucci PM, Garagiola I, et al. A randomized trial of factor VIII and neutralizing antibodies in hemophilia A. N Engl J Med 2016;374:2054-64. DOI: 10.1056/NEJMoa1516437

TABLE OF CONTENTS

LIST OF PARTICIPANTS

SIPPET investigators (in order of number of randomized patients): A. El-Beshlawy, S.A. Habib and N. Omar, Pediatric Hematology Department, Cairo University Pediatric Hospital, Cairo, Egypt (38 patients); M. Elalfy and N. Elbarbary, G. Nevine and S. Abdelghani, Faculty of Medicine, Ain Shams Center, University - Department Pediatrics, Cairo, Egypt (38 patients); V. Ramanan and S. Lohade, Jehangir Clinical Development Centre, Department of Hematology, Jehangir Hospital Premises, Pune, India (22 patients); P. Eshghi, M. Ahmadinejad and B.H. Panah, Congenital Pediatric Hematologic Disorders Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran (19 patients); S. Hanagavadi, M.S. Hanagavadi and M. Kumar, J J M Medical College, Davangere, India (15 patients); R. Varadarajan, Centre for Blood Disorders, Chennai, India (15 patients); M. Karimi, A. Afrasiabi and Z. Zahedi, Hematology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran (13 patients); M.V. Manglani and S.M. Sharma, Lokmanya Tilak Municipal Medical College & General Hospital, Sion, Mumbai, India (9 patients); C. Ross and S. Subramanian, St. John's Medical College Hospital, Bangalore, India (8 patients); G. Young, Children's Hospital Los Angeles (CHLA), Los Angeles, USA (8 patients); T. Seth and R. Saxena, All India Institute of Medical Sciences, Department of Hematology, New Delhi, India (7 patients); S. Apte and S. Kannan, Sahyadri Speciality Hospital, Pune, India (6 patients); D.M. Nayak and A. Kurien, Melaka Manipal Medical College (Manipal campus), Manipal University, Karnataka, India (6 patients); E. Santagostino and M.E. Mancuso, Angelo Bianchi Bonomi Hemophilia and Thrombosis Centre, IRCCS Ca' Granda Maggiore Policlinico Hospital Foundation, Milan, Italy (6 patients); A.C. Sandoval Gonzales and M.T. Pompa, Hospital de Especialidades UMAE, Istituto Mexicano del Seguro Social (IMSS), Monterrey, Mexico (5 patients); J.N. Mahlangu and R. Schwyzer, Faculty of Health Sciences, School of Pathology; University of the Witwatersrand, NHLS and Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa (4 patients); S. Bonanad and S. Haya, Hospital Universitario La Fe, Unidad Coagulopatias Congenitas, Valencia, Spain (3 patients); M. Cerqueira and A.P. Marques, Centro de Pesquisa Clinica HEMORIO - Instituto Estadual de Hematologia Arthur de Siqueira Cavalcanti, Rio de Janeiro, Brazil (3 patients); N.P. Ewing and C. DeGuzman, City of Hope National Medical Center, Duarte, California, USA (3 patients); C. Male and K. Thom, Medizinische Universität Wien, Department of Paediatrics, Wien, Austria (3 patients); T. Owaidah and M.M. Saleh, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia (3 patients); V. Soto Arellano and D. Cortez Salazar, Centro de Hemofilicos del Hospital de Niños Dr. Roberto del Rio, Santiago, Chile (3 patients); N.L. Kobrinsky, Sanford Roger Maris Cancer Center, Fargo, North Dakota, USA (2 patients); S. Majumdar, University of Mississipi Medical Center, Division of Pediatric Hematology/Oncology, Jackson, Mississippi, USA (2 patients); R. Perez Garrido and R. Nuñez Vazquez, Hospital Universitario Virgen del Rocio, Unidad de Hemofilia, Sevilla, Spain (2 patients); A. Sachdeva and N. Radhakrishnan, Pediatric Hematology Oncology and Bone Marrow Transplantation Institute For Child Health Sir Ganga Ram Hospital, New Delhi, India (2 patients); M. Simpson, Rush Hemophilia & Thrombophilia Center, Rush University Medical Center, Chicago, Illinois, USA (2 patients); M. Thomas, Kerala lnstitute of Medical Science, Kerala, India (2 patients); E. Zanon and M. Milan, Clinica Medica II, Azienda Ospedaliera di Padova, Centro Emofilia, Padova, Italy (2 patients); B. Antmen and I. Sasmaz, Cukurova Universitesi, Tip Fakultesi Pediatrik

Hematoloji B.D., Adana, Turkey (1 patient); K. Kavakli, Ege Universitesi Tip Fakultesi Cocuk Sagligive Hastalikari Anabilim Dali, Pediatrik Hematoloji Bilim Dali, Izmir, Turkey (1 patient); M.J. Manco-Johnson, Hemophilia & Thrombosis Center, University of Colorado Denver, Aurora, Colorado, USA (1 patient); M. Martinez, Hospital de Ninos Sor Maria Ludovica La Plata, Servicio de Hematologia, Buenos Aires, Argentina (1 patient); E. Marzouka, Hospital de Ninos Dr. Luis Calvo Mackenna, Centro Hemofilico, Santiago, Chile (1 patient); M.G. Mazzucconi and C. Santoro, Ematologia, UO Diagnostica Speciale e Terapia delle Malattie dell'Emostasi e della Trombosi, Università Sapienza, Policlinico Umberto I, Rome, Italy (1 patients); D. Neme and L. Elhelou, Fundación de la Hemofilia, Buenos Aires, Argentina (1 patient); A. Palomo Bravo, Hospital Regional Universitario Carlos Haya, Malaga, Spain (1 patient); R. Paredes Aguilera, Instituto National de Pediatria, Ciudad de México, Mexico (1 patient); A. Prezotti, Centro de Hematologia e Hemoterapia do Espírito Santo - Hemoes, Vitoria, Brazil (1 patient); K. Schmitt and R. Schwarz, Department of Pediatric and Adolescent Medicine, Kepler University Clinic, Linz, Austria (1 patient); B.M. Wicklund, Children's Mercy Hospital, Kansas City, Missouri, USA (1 patient); B. Zulfikar and B. Koç, Istanbul Universitesi Cerrahpasa Tip Fakultesi, Pediatrik Hematoloji B.D., Istanbul, Turkey (1 patient).

SIPPET Steering Committee: P.M. Mannucci, Angelo Bianchi Bonomi Hemophilia and Thrombosis Centre, IRCCS Ca' Granda Maggiore Policlinico Hospital Foundation, Milan, Italy (principal investigator); F. Peyvandi, Angelo Bianchi Bonomi Hemophilia and Thrombosis Centre, IRCCS Ca' Granda Maggiore Policlinico Hospital Foundation, and Department of Pathophysiology and Transplantation, University of Milan, Milano, Italy (principal investigator); S. Apte, Sahyadri Speciality Hospital, Pune, India; J.A. Aznar, Grupo de Hemostasia, Trombosis Arteriosclerosis y Biologia Vascular, Hospital Universitario y Politecnico La Fe, Valencia, Spain; H. Chambost, La Timone Children Hospital APHM, Aix Marseille University, Marseille, France; J. Goudemand, Institut d'Hématologie, Hôpital Cardiologique, Lille, France; W. Kreuz, Klinikum der Johann Wolfgang Goethe-Universität, Zentrum für Kinderheilkunde III, Päd. Hämatologie, Onkologie und Hämostaseologie, Frankfurt am Main, Germany; R. Kruse-Jarres, Washington Center for Bleeding Disorders, Blood Works NW, Seattle, Washington, USA; J.N. Mahlangu, Faculty of Health Sciences, School of Pathology; University of the Witwatersrand, NHLS and Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa; M. E. Mancuso, Angelo Bianchi Bonomi Hemophilia and Thrombosis Centre, IRCCS Ca' Granda Maggiore Policlinico Hospital Foundation, Milano, Italy; C. Négrier, Louis Pradel Hospital, University Claude Bernard Lyon, France; E. Santagostino, Angelo Bianchi Bonomi Hemophilia and Thrombosis Centre, IRCCS Ca' Granda Maggiore Policlinico Hospital Foundation, Milano, Italy; M. Tarantino, Bleeding and Clotting Disorders Institute, Peoria, Illinois, USA.

SIPPET Data Safety Monitoring Board (DSMB): L.M. Aledort, Mount Sinai School of Medicine, New York, New York, USA; A.R. Giles, Divisions of Hematopathology & Hematology, Depts. Pathology & Molecular Medicine & Medicine Richardson Laboratory, Queen's University Kingston, Ontario, Canada; G-E. Rivard, Division of Hematology, Sainte-Justine Hospital, Montreal, Canada.

METHODS: INTERIM ANALYSIS

An interim analysis was performed according to a prespecified analytical plan to be evaluated by the DSMB. The analysis was performed independently from the Milan principal investigators and the Steering Committee and submitted to the DSMB, who advised to continue the study. This analysis was done when 204 patients had been randomized.

TABLE S1. FOLLOW UP IN PATIENTS WHO DID NOT DEVELOP INHIBITOR.

	Randomized to plasma-derived FVIII ***(96)***	**Randomized to recombinant FVIII** (79)
Early termination, n (%)	4 (4,2%) (median ED = 25; range 20-29)	6 (7,6%) median ED = 25,5; range 8-45
3 years from randomization, n (%)	29 (30,2%) (median ED = 22; range 4-44)	23 (29,1%) median ED = 15; range 1-35
≥50 ED, n (%)	50 (52,1%)	40 (50,6%)
21-49 ED, n (%)	1 (1,0%)	1 (1,3%)
1-20 ED, n (%)	12 (12,5%)	9 (11,4%)

TABLE S2. ADJUSTED HAZARD RATIOS FOR RECOMBINANT VS PLASMA-DERIVED FACTOR VIII, FOR ALL INHIBITORS.

Adjustment variable	**Hazard ratio (95% confidence interval)**
None	1.87 (1.17-2.96)
Age	1.88 (1.18-2.99)
Mutation	1.97 (1.22-3.17)
Country 5 categories 14 categories	 1.89 (1.19-3.00) 1.88 (1.17-3.01)
Ethnicity	1.87 (1.18-2.97)
Family history of hemophilia	1.82 (1.14-2.89)
Family history of inhibitor	1.66 (1.03-2.67)
Previous exposure blood components	1.86 (1.17-2.95)
Treatment regimen	1.82 (1.15-2.90)
Treatment intensity	1.87 (1.17-2.97)
Surgery	1.80 (1.13-2.86)

TABLE S3. COX REGRESSION RESTRICTED TO COUNTRIES WHERE KOGENATE WAS NOT USED.

Adjustment variable	Hazard ratio (95% confidence interval)
All inhibitors	
None	1.98 (0.99-3.97)
Age, mutation	2.03 (0.96-4.30)
High-titre inhibitors	
None	2.59 (1.11-6.00)
Age, mutation	2.61 (1.06-6.41)

TABLE S4. SEVERE ADVERSE EVENTS.

	Randomized to plasma-derived FVIII, n (n of patients who developed inhibitor)	Randomized to recombinant FVIII, n (n of patients who developed inhibitor)
Death	2 (0)	0
Intracranial bleeding		
Intracerebral	2 (1, high titer)	3 (0)*
Subdural	1 (1, high titer)	2 (1, high titer)
Epidural	1 (0)	0
Gastrointestinal bleeding	1 (0)	1 (1, low titer)

* All patients were on an on-demand regimen, except one patient who developed intracerebral bleeding who was receiving prophylactic treatment