

Supplementary Appendix

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

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SUPPLEMENTAL APPENDIX

List of sites by country in order of enrollment.

Argentina (84) - *Fundacion Colombo Diaz* (20) - N. Garcia; *Centro del Rinon y Dialisis S.A.* (15) - A. Penalba; *Fundacion J. Robert Cade* (14) - L.Juncos; *Instituto de Cardiologia de Corrientes Juana Francisca Cabral* (7) -S. Maurich; *Sanatorio Allende* (7) - M. Orias; *IME Insituto Medico especializado* (6) - F. Margulis; *CEREHA* (4) - H. Beresan; *Hospital Italiano de Buenos Aires* (3) - G. Rosa-Diez; *Hospital General de Agudos Dr. Cosme Argerich* (3) - A. Vallejos; *Centro de Educacion Medica e Investigaciones Clinicas- CEMIC* (2) - A.M. Cusumano; *Hospital Privado-Centro Medico of Cordoba* (2) - W. Douthat; *Hospital Aeronautico* (1) - A. Carreno; **Australia (58)** - *Simon Roger's Consulting Rooms* (25) - S. Roger; *Liverpool Hospital* (7) - M. Suranyi; *Launceston General Hospital* (5) - M. Mathew; *Lyell McEwin Health Service* (5) - W. Jeffries; *Austin Health, Repatriation Hospital* (3) - G. Jerums; *Bawon Health, Geelong Hospital* (3) - G. Nicholson; *The Queen Elizabeth Hospital* (3) - G. Russ; *Sir Charles Gairdner Hospital* (2) - B. Hutchison; *Princess Alexandra Hospital* (2) - D. Johnson; *Royal Hobart Hospital* (2) - M. Jose; *Royal Adelaide Hospital* (1) - D. Torpy; **Austria (3)** - *Medizinische Universität Graz* - H. Toplak; *Medizinische Universität Wien* - W. Hörl; *SALK- B. Paulweber*; **Brazil (190)** - *Centro Integrado de Diabetes e Hipertensao* (30) - A. Forti; *Oswaldo Ramos Foundation, Federal Univ of Sao Paulo* (20) - M.E. Canziani; *Faculdade de Medicina Federal da Universidade de Ceara* (20) - R. Montenegro; *Faculdade de Ciencias Medicas de Sorocababa - Hospital Santa Lucinda da pontificia Universidade Cato* (15) - F.A. Almeida; *Hospital de Base - Faculdade de Medicina de Sao Jose do Rio Preto* (13) - E. Burdmann; *Universidade Estadual de Campinas* (9) - J.B. Lopes de Faria; *Instituto de Urologia e Nefrologia* (8) - M.A. Sperto Baptista; *Nefroclinica de Uberlandia Ltda* (7) - S.R. Ferreira Filho; *Santa Casa Porto Alegre e FFFCMPA* (7) - H. Schmid; *Centro de Pesquisas em Diabetes* (6) - J. Luiz Gross; *Hospital Geral do Bonsucesso* (6) - D.B. Monteiro Carvalho; *Centro de Tratamento Renal* (6) - S. Neiva Coelho; *Catholic University of Parana, Curitiba, Brazil* (6) - M.C. Riella; *Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo* (4) - H. Abensur; *Fundacao IMEPEN* (4) - M. Bastos; *Hospital São Lucas da Pontificia Universidade Catolica do Rio Grande do Sul* (4) - D. d'Avila; *Hospital Universitario Antonio Pedro* (4) - J. Lugon; *Instituto Dante Pazzanese* (3) - J.C.M. Moreira; *Hospital Universitario da Universidade Federal do Maranhao* (3) - N. Salgado; *Hospital Sao Rafael* (2) - P.B.P. Batista; *Universidad Federal do Rio de Janeiro* (2) - A.G. Delgado; *Beneficencia Portuguesa de Sao Paulo* (2) - I. Noronha; *Instituto Capixaba de Doencas Renais e Hipertensao* (2) - L. Vasconcelos; *Hospital de Clinicas de Porto Alegre* (1) - E. Barros; *Hospital Universitario Prof Edgard Santos – UFBA* (1) - R. Martinelli; *Hospital das Clinicas da Faculdade de Medicina de Ribeirao Preto da Universidade de Sao Paulo* (1) - M. Moyses Neto; *Universidade Santo Amaro / UNISA / NEFROCOR* (1) - L. Yu; *Hospital Heliopolis/CP Clin-Centro de Pesquisas Clinicas* (1) - F. Eliaschewitz; *Hospital Universitário Cassiano Antonio Moraes* (1) - L. Vasconcelos; *Hospital e Maternidade Celso Pierro - PUC Campinas* (1) - J.F.K. Saraiva; **Bulgaria (28)** - *Multicenter Hospital for Active Treatment, Stara Zagora (MHAT)* (11) - T. Mircheva; *Multicenter Hospital for Active Treatment, Sveta Anna (MHAT)* (11) - A. Angelova; *Multicenter Hospital for Active Treatment, Prof. St. Kirkovich (MHAT)* (3) - M. Doncheva; *Uni Multiprofile hospital for active treatment* (3) - H. Hristozov; **Canada (176)** - *Sheldon M. Chumir Health Centre* (23)- N. Scott-Douglas, B. Culleton; *Chow, Stephen MD* (22) - S. Chow; *Clinical Research Consultant Group* (13) - A. Dowell; *Sunnybrook*

Health Sciences Centre (12) - S. Tobe; Daniel Sapir Medicine Professional Corp (12) - D. Sapir; Centre Hospitalier Universitaire de Laval (9) - S.J. Weisnagel, A. Nadeau; Credit Valley Hospital (7) - G. Wong; Royal Inland Hospital (7) - E. Wijeyesinghe; Tanaka, Roderick MD (6) - R. Tanaka; University of Ottawa Heart Institute (5) - H. Haddad; Institut de Cardiologie de Montréal (5) - A. Ducharme; Gordon and Leslie Diamond Health Care Centre (4) - T. Elliott; Northern Alberta Renal Program, University of Alberta Hospital, Department of Medicine (4) - K. Jindal; Atlantic Health Sciences Corporation (4) - P. Sohi; Eastern Health - General Site (4) - P. Parfrey; Kajbaf, Sahar MD (4) - S. Kajbaf; Queen Elizabeth II Health Sciences Centre (3) - S. Soroka; Centre de Recherche Clinique de Laval (3) - A. Belanger; London Health Science Centre (3) - N. Muirhead; Oshawa Clinic (3) - D. Birbrager; St. Michael's Hospital (3) - P. McFarlane; St. Joseph's Healthcare (2) - C. Rabbat, D. Churchill; Saskatoon Nephrology Group (2) - G. Pylypchuk; LMC Endocrinology Centres (2) - R. Goldenberg; LMC Endocrinology Centres (2) - Y. Twum-Barima; Regina General Hospital (2) - S. Karunakaran; Keele Medical Place (2) - J. Sussman; Hôpital du Sacré-Coeur de Montréal (2) - D.I Bichet; CHUM Hotel Dieu de Montreal (1) - J.-M. Ekoe; Jolly, Shivinder MD (1) - S. Jolly; Southern Alberta Renal Program (1) - M. Wong; Innes, Dr. Peter MD (1) - P. Innes; LMC Endocrinology Centres (1) - R. Aronson; The Bailey Clinic (1) - G. Bailey; **Chile (14)** – CLINDIAL (5) - A. Castillo; Laboratorio de Nefrologia Universidad Austral de Chile, Hospital Regional Valdivia (4) - S. Mezzano; Hospital Regional de Temúco (3) - M. Calderara; Dial-Sur (2) - J. Becker; **Czech Republic (96)** - Institut klinicke a experimentalni mediciny (18) - F. Saudek; Nemocnice Sternberk (14) - B. Lacnak; Oblastni nemocnice Kladno, a.s.(12) - J. Povolny; Nemocnice Prostejov (11) - M. Marsová; Fakultni Nemocnice Kralovske Vinohrady (6) - I. Rychlík; Poliklinika NHO (5) - E. Racicka; Nemocnice Nové Mesto na Morave (5) - I. Mácel; Soukroma Ambulance (5) - P. Chmura; Nemocnice Litomyslska (5) - M. Dunaj; Fakultni Nemocnice Pizen (4) - J. Hirmerová; Nemocnice Jihlava (4) - J. Tocik; Fakultni Nemocnice Hradec Králové (3) - A. Smahelová; Fakultni Nemocnice Olomouc (2) - J. Záhalková; Fakultni Nemocnice V Motole (2) - M. Kvapil; **Denmark (10)** - Roskilde Amtssygehus (5) - O. Oestergaard; Steno Diabetes Center (4) - P. Rossing, H.H. Parving, University of Fredriksberg Hospital (1) - S. Urhammer; **Estonia (16)** - Estonia Diabetes Centre (6) - M. Past; University of Tartu (4) - M. Rosenberg; Viljandi Hospital (4) - H. Vides; Parnu Diabetes Outpatient Centre (1) - L. Viitas; West Tallinn Central Hospital (1) - M. Ilmoja; **France (11)** - Ctre Hospitalier Universitaire de Grenoble (5) - P. Zaoui; Hopital E Herriot (4) - J.-P. Fauvel; Centre Hospitalier Robert Bisson (2) - L. Geffray; **Germany (135)** - Praxis Dr. Kraatz - U. Kraatz; Gemeinschaftspraxis Karlstrasse - F. Dellanna; Diabetologische Schwerpunktpraxis- K. Busch; KfH Nierenzentrum Greifswald- G. Kraatz; Praxis Dr. Voßkübler - A. Voßkübler; Klinikum Hannover-Oststadt - R. Brunkhorst; Forschungszentrum Ruhr- A. Eckartz; Universitätsklinikum Ulm - F. Keller; Dialysezentrum Dormagen - L. Merker; Marienhospital Herne - D. Rattensperger, L.-C. Rump; Dialysezentrum Würzburg - L. Schramm; Medizinische Hochschule Hannover - H. Haller; Carl-Thiem-Klinikum Cottbus GmbH - H. Steinhauer; Universitätsklinik Erlangen - K.-U. Eckardt; Gemeinschaftspraxis - G. Klausmann; Gemeinschaftspraxis - G.-P. Dragoun; Evangelisches Krankenhaus Herne - W. Sehnert; Klinikum der Universität Regensburg - A. Schäffler; Kerckhoff-Klinik der Max-Planck-Gesellschaft - V. Mitrovic; Universitätsklinikum Göttingen - G. Müller; Klinikum Schwalmstadt - R. Zotz; **Hungary (70)** - District Hospital Szigelvár (15) - C. Salamon; Pandy Kalman County Hospital (11) - M. Dudas; Dr. Rethy Pal Korhaz-Rendelointezet (7) - A. Gyimesi; Drug Research Center Kft. (7) - L. Koranyi; Zala Megyei Korhaz (7) - T. Oroszián; Flór Ferenc Hospital (7) - K. András; Szent Ferenc Hospital (6) - G. Andrassy; District Hospital Slófok (3) - K. Simon;

Csolnok Ferenc County Hospital (2) - G. Vándorfi; Gottsegen Gyorgy Orszagos Kardiologiai Intezet (2) - M. Keltai; Markusovszky County Hospital III (2) - L. Nagy; PECS University (1) - J. Nagy; **Italy (87)** - Azienda Ospedaliera di Lecco (14) - F. Locatelli; Università degli Studi di Bari (10) - P. Coratelli; Azienda Ospedaliera Federico II (7) - B. Cianciaruso; Fondazione Salvatore Maugeri (5) - G. Villa; Ospedale San Giovanni Bosco (5) - F. Quarello; Presidio Ospedaliero S.Felice a Canello (5) - M. Apperti; Seconda Università di Napoli, Policlinico Nuovo (4) - G. Capasso; Ospedale S. Leonardo (4) - M. Auricchio; Azienda Ospedaliera Pugliese-Ciaccio (4) - L. Lombardi; Ospedale San Martino (4) - G. Viviani; Ospedale Niguarda Cà Granda (4) - G. Colussi, G. Busnach, G. Civati; Policlinico Universitario (3) - G. Bellinghieri; Ospedale Vito Fazzi (3) - E. Buongiorno; Università degli studi di Bari-Policlinico (3) - F.P. Schena; Istituto Clinico "Humanitas" (3) - E. Gronda; Presidio Ospedaliero di Piedimonte Matese (2) - S. Coppola; Ospedali Riuniti di Bergamo (2) - G. Remuzzi; Policlinico San Matteo (2) - A. Dal Canton; Azienda Ospedaliera di Perugia (Silvestrini) (1) - U. Buoncristiani, R. Fagugli; Ospedale San Martino (1) - G. De Ferrari; Nuovo Ospedale Versilia (1) - F.P. Ferranello; **Latvia (51)** - P Stradina Clinical University Hospital (12) - V. Pirags; P Stradina Clinical University Hospital (8) - J. Romanova; Riga Eastern Clinical University Hospital, Clinic Gailezers (6) - A. Grigane; Liepaja Central Hospital (6) - A. Lucenko; Riga Eastern Hospital, Daugavpils Regional Hospital (6) - J. Sokolova; P Stradina Clinical University Hospital (5) - A. Petersons; Valmieras Hospital (2) - B. Jegere; Ogres City Clinic (2) - D. Teterovska; Riga Eastern Clinical University Hospital, Clinic Gailezers (2) - A. Valtere; Diabetes Center (1) - I. Stelmane; Ventspils City Hospital (1) - U. Zviedritis; **Mexico (150)** - Hospital Pedro Loza Cardiologia (19) - A. Lopes Alvarado; Hospital General de Zona # 6 IMSS (14) - R.R.Rico Hernandez; Hospital Centenario Miguel Hidalgo (13) - A. Chew-Wong; Unidad de Investigacion Clinical Fresenius Medical Care (12) - T. Bochicchio-Ricardelli; Hospital Christus Muguerza (12) - G. Ramirez; Instituto de Investigaciones Medicas, Univ. de Guanajuato (11) - C. Kornhauser-Araujo; Nefrologia y Dialisis de San Luis S.C (10) - J. Ramos; Hospital Regional "Dr Valentin Gomez Farias" (ISSSTE) (9) - H.S. Breien-Alcaraz; FMC Medica Sur (9) - R. Correa-Rotter; Hospital Civil de Guadalajara "Doctor Juan I. Menchaca" (9) - G. Gonzalez-Galvez; Centro Medico "La Concepcion" (7) - M.G. Melo-Sanchez; Hospital Ramon Santiago y Cajal (5) - R. Cuellar-Gonzalez; Hospital Juarez de Mexico SA de CV (5) - M. Vital; Investigacion en Factores de Riesgo Cardiovascular Omega S.C. Omega (4) - H. Sanchez; Instituto Nacional de Cardiologia Doctor Ignacio Chavez Rivera, Servicio de Nefrologia (3) - M. Guevara, J.P. Herrera; Hospital Angel Leano (3) - F. Flores; Centro Medico Dalinde, Universidad Panamericana (2) - G. Obrador; Star Medica (2) - F.E. Quintana-Pina; Hospital San Jose Tec de Monterrey (1) - A. Valdes; **Poland (213)** - Voivoidship Hospital (30) - J. Felisiak; Niepubliczny Zaklad Opieki Zdrowotnej "Atopia" (24) - G. Pinis; Wojewodzki Szpital Specjalistyczny (17) - B. Kusnierz; Central Clinical Hospital SPZOZ Miedzylesie (13) - R. Malecki; Bydgoszczs Diabetology & Endocrinology Centre (12) - M. Polaszewska-Muszynska; PSZOZ Inowroclaw (10) - M. Bronisz; Military Hospital (10) - P. Ponikowski; Wojew Szpital Zespolonu im L Rydygiera (9) - M. Muszytowski; University Hospital of Krakow (8) - W. Sulowicz; Specialistic Hospital (7) - R. Szelemej; Szpital Morski im. PCK (7) - M. Szpajer; Niepubliczny Zaklad Opieki Zdrowotnej (NZOZ) Stacja Dializ Sp. z o.o. (7) - R. Trafny; Wojewodzki Szpital Brodnowski (6) - M. Dluzniewski; Samodzielny Publiczny Szpital Kliniczny nr 1, im. Prof. Stanislaw Szyszko (6) - W. Grzeszczak; Klinika Chorob Wewnetrznych i Nefrologii, CSK MSWiA (5) - A. Rydzewski; District Hospital (5) - C. Bloch; Miejski Szpital Zespolony (4) - K. Janik; Gdanska Poradnia Cukrzycowa (4) - P. Romanczuk; Szpital Miejski im. J.Brudzinskiego (3) - P. Miekus; Uniwersytecki Szpital Kliniczny w Bialymstoku (3) - W. Musial;

Cardiac Centre AMICOR (3) - W. Piotrowski; Szpital Specjalistyczny im. Rydygiera (3) - O. Smolenski; SPSW Hospital (3) - K. Marczewski; Samodzielny Publiczny Szpital Kliniczny (2) - J. Dulawa; Samodzielny Publiczny Zakład Opieki Zdrowotnej w Lubartowie (2) - A. Gieroba; Wojewodzki Szpital Specjalistyczny (2) - Z. Hruby; Samodzielny Szpital Wojewodzki (2) - M.I. Ogorek; Niepubliczny Zakład Opieki Zdrowotnej (NZOZ) Medi-Diab (2) - A. Siegel; Wojewodzki Hospital (2) - M. Janion; Wojewodzki Szpital Zespólny (1) - Z. Gozdzik; Pieporka Marek, MD (1) - M. Piepiorka; **Portugal (17)** - Hospital de São Bernardo, SA (9) - J.M. Vinhas; Hospital De Sao Joao, EPE (4) - M. Pestana; Hospital Distrital de Faro (2) - A.P. Silva; Hospital Fernando da Fonseca Amadora/Sintra (1) - P. Correia; Hospital Santa Cruz (1) - M. Pais; **Romania (47)** - Fundeni Clinical Institute (23) - M. Voiculescu; Emergency Clinical Hospital Bucharest (9) - L. Ardelean; Diabmed Dr. Popescu Alexandrina Srl' Private Clinic (5) - A. Popescu; Emergency County Clinical Hospital Timisoara (4) - G. Gluhovschi; Prof.Dr. Ioiart Private Clinic (3) - R. Ioiart; University Hospital, Internal Medicine Clinic (2) - D. Olteanu; Dr. Carol Davila Nephrology Clinical Hospital (1) - G. Mircescu; **Russia (117)** - Saint-Petersburg State Medical University named after I.P.Pavlov, Nephrology Research Institute (16) - V. Dobronravov; Multiple-discipline City Hospital #2 (14) - A. Zalevskaya; State Institution Endocrinological Research (10) - M. Shestakova; City Diagnostics Centre 1, Saint-Petersburg Diabetological Center (9) - I. Karpova; Moscow State Institute of Public Health, Hospital for Veteranov Wars #2 (9) - G. Volgina; State Healthcare Institution Goroda Moscv, City Clinical Hospital Named after S.P.Botkin (7) - E. Zakharova; Yaroslavl State Medical University, Clinical Pharmacology based at City Clinical Hospital N2 (7) - A. Khokhlov; Saint-Petersburg State Medical Academy Named after I.I.Mechnikov Roszdrava (6) - E. Kolmakova, M. Komandenko; Moscow State Institution of Public Health City Clinical Hospital #52 (6) - N. Tomilina; State Medical Institution Sverdlovsk Regional Clinical Hospital N1 (5) - N. Klimusheva; The State Saint-Petersburg' institution of public health "City Mariinsky Hospital" (4) - G. Shostka; The Federal State institution named after N.I.Pirogov, Roszdrava (4) - V. Anashkin; Moscow Medical Academy named after I.M. Sechenov (4) - Y. Milovanov; Municipal Health Care Institution Municipal Clinical Hospital N40 (4) - A. Nazarov; Yaroslavl Regional Clinical Hospital (3) - O. Khrustalev; Yaroslavl Municipal Healthcare Institution, Clinical Hospital for Emergency Care n.a. N.V. Solovyov (3) - V. Yakusevich; Central Clinical Hospital N1 of Russian Railways (3) - A. Dmitriev; Medical Military Academy named after S.M.Kirov, First Clinic of Therapy of Postgraduate (2) - S. Choustov; State Healthcare Institution Goroda Moskvi, City Clinical Hospital #20 (1) - V. Shilo; **Slovakia (65)** - Nefrologicka ambulancia, SMOLKO s.r.o. (21) - P. Smolko; Faculty Hospital Dolny Kubin (14) - E. Hrudova; Fakultná nemocnica Nitra (9) - J. Sirotiakova; Logman a. s. (7) - I. Jankechova; Fakultna nemocnica Tmav (6) - J. Hromec; Logman a.s. (4) - P. Javorsky; Fakultna nemocnica L. Pasteura Kosice, Urologicka klinika (3) - I. Tkac; Policilinic Sever (1) - K. Suchozova; **Slovenia (12)** - Splosna Bolnisnica Celje (6) - M. Preloznik; Splosna Bolnisnica Maribor (3) - R. Hojs; Splosna Bolnisnica Nova Gorica (2) - S. Saksida; Splosna Bolnisnica Jesenice (1) - I. Rus; **United Kingdom (49)** - Kings College Hospital (15) - I. Macdougall; Royal Free Hospital (7) - A. Burns; Royal United Hospital (5) - J. Reckless; York District Hospital (3) - P. Jennings; Southmead Hospital (3) - R. Smith; Addenbrooke's Hospital (2) - N. Pritchard; Royal Glamorgan Hospital (2) - M. Page; Lister Hospital (2) - L. Borthwick; Whipps Cross University Hospital (2) - D. Levy; North Manchester General Hospital (2) - M. Savage; Birmingham Heartlands Hospital (2) - I. Dasgupta; Northern General Hospital NHS Trust (1) - S. Heller; University of Glasgow (1) - J. McMurray; Diana Princess of Wales Hospital (1) - F. Abourawi; Queens Medical Centre (1) - S. Page; **USA (2339)** - Coastal Nephrology Associates

Research Center (50) - K. Kaveh; *Advanced Kidney Specialist* (45) - S. Sarkar; *Renal Physicians Inc.* (39) - R. Dhingra; *Carolina Pharmaceutical Research* (35) - J. Moran; *Chrishard Medical Group* (34) - C. Scott; *South Carolina Nephrology & Hypertension* (34) - M. Moustafa; *Kansas City VA Medical Center* (27) - T. Wiegmann; *Kidney Care Associates, LLC* (24) - J. Hertel; *Plaza Medical Group* (24) - C. Sholer; *UT Southwestern Medical Center (West Campus)* (24) - R. Saxena; *Smith Clinic Research* (23) - M. Comianos; *Physicians East PA* (23) - M. Warren; *Columbia Nephrology Associates, P.A.* (22) - J. Buerkert; *Pottstown Medical Specialists, Inc* (22) - S. Vaisman; *Diversified Medical* (21) - P. Salvato; *DaVita/USC Kidney Center* (20) - M. Akmal; *Tri-State Medical Group* (19) - T. Jackson; *Nelson, Mark W, MD* (19) - N. Goldberg; *Southeast Texas Cardiology Associates, LLP* (18) - R. Sotolongo; *Bay Pines Foundation, Inc.* (18) - U. Shettigar; *Genesis Clinical Research* (17) - J. Navarro; *Jacksonville Heart Center* (17) - T. Hilton; *Boise Kidney and Hypertension Institute* (17) - A. Sharma; *Thrasher, James MD Inc* (17) - J. Thrasher; *Pioneer Medical Group* (17) - S. Patel; *Riverwood Medical Associates* (17) - B. Scanlan; *Hypertension and Nephrology, Inc.* (16) - R. Cottiero, M. Weinberg; *Forsyth Hematology/Oncology* (16) - S. Moore; *Palmetto Nephrology, PA* (16) - M. Nassri; *Northwest Nephrology Associates, PA* (16) - R. Malya; *Arms Dodge Robinson Wilber & Crouch, Inc* (15) - T. Crouch; *Metropolitan Research* (15) - R. Cheriyan; *Apex Medical Research, AMR, Inc.* (15) - A. Ahmed; *Sacramento Medical Research Center* (15) - T. Awan, N. Awan; *San Antonio Kidney Disease Center* (15) - C. Hura; *Hypertension and Renal Research Group* (15) - T. Herman; *Clark Family Medicine* (14) - B. Clark; *Kaplan and Kaplan* (14) - I. Kaplan, M. Kaplan; *Patients First Health Care* (14) - G. Dumontier; *James A. Haley Veterans Hospital* (14) - A. Peguero, A. Hung; *University of Texas, Health Science Center-San Antonio* (14) - A. Shepherd; *International Clinical Research Network, Inc* (14) - G. Argoud; *Dom Research Institute* (13) - A. Saenz, H. Yu; *Pines Clinical Research, Inc.* (13) - S. Zeig; *Kidney and Medical Specialists, PC* (13) - D. Santacruz; *Louisiana State University Health Sciences Center* (13) - J. Blondin; *The Heart Center* (13) - J. Smelser; *Bluefield Regional Medical Center* (13) - M. Sekkarie; *Cesar Albarracin MD PA Research Inc* (13) - C. Albarracin; *Therapeutic Research Institute of Orange County* (13) - J. Daigneault; *Advance Medical Research* (13) - J. Rubin; *Kidney and Hypertension Specialist-Clinical Research Solutions* (13) - B. Bhatla; *Hawthorn Medical Associates* (13) - A. Altschuller; *Tri-State Medical Group-Internal Medicine Specialists* (12) - G. Walker; *Renal Associates of Baton Rouge* (12) - M. Roppolo; *Vernon Medical Center* (12) - J. Singh; *Strong Cardiology Associates* (12) - J. Bisognano, C.-S. Liang; *VA Greater LA Health Care Services - West LA* (12) - S. Levin; *Green Clinic, LLC* (12) - M. Nammour; *Gaona, Raul E* (12) - R. Gaona; *Arroyo Research Inc* (12) - S. Farag, H. Sideropoulos; *Tampa Bay Medical Research, Inc.* (12) - P. Denker; *Nephrology Private Practice* (12) - J. Cangiano; *Corsicana Medical Research, PLLC* (11) - S. Shafik; *University of Kansas Medical Center, Research Institute* (11) - A. Chonko; *G Edward Newman MD, PLLC* (11) - G.E. Newman; *Michigan Institute of Medicine PC* (11) - K. Pierce; *Philadelphia Health Associates-Adult Medicine* (11) - J. Shapiro; *Jacobi Medical Center* (11) - A. Acharya; *Advance Medical Research* (11) - M. Perley; *PAB Clinical Research* (11) - K. Kapatkin; *Goswami, Atul MD* (11) - A. Goswami; *Preferred Primary Care Physicians* (11) - P. Hartley; *New York Department of Veterans Affairs Medical Center* (10) - D. Goldfarb; *Durham Internal Medicine Associates* (10) - C. Gifford, J. Kelly; *Salem VA Medical Center* (10) - A. Iranmanesh; *David Ramstad, MD, MPH and Associates* (10) - D. Ramstad; *Scripps Clinic* (10) - A. King; *Leddy, Vincent L MD* (10) - V. Leddy; *Ohio State Univ Medical Ctr* (10) - A. Agarwal; *Internal Medicine Associates* (10) - D. Colan; *Minneapolis Veterans Affairs Medical Center* (10) - I. Anand; *Pharmaceutical Research Associates Inc* (10) - B. Walls; *Diabetes and Endocrine*

Center (10) - M. Amar; *St Louis University* (10) - D. Janosik, F. Bleyer; *James A. Campbell Jr. and Associates* (10) - J. Campbell; *Nephrology Private Practice* (10) - L. Quesada-Suarez; *Kandra Frier Kuskin Associates, LTD* (9) - R. Fierer; *Northwest Louisiana Nephrology LLC* (9) - R. Zabaneh; *Nephrology Associates of Orlando* (9) - U. Ranjit, T. Youell; *Texas Tech University Health Sciences Center- Division of Clinical Research* (9) - S. Prabhakar; *Hudson Valley Cardiology Group* (9) - G. Hamroff; *Harrisburg Family Medical Center* (9) - V. Houchin; *Cherlin, Richard MD* (9) - R. Cherlin; *Glendale Kidney Center* (9) - R. Minasian; *University of California at Davis* (9) - R. White; *Northwest Indiana Center for Clinical Research* (9) - R. Buynak; *Stamford Nephrology* (8) - E. Brown; *Hypertension and Nephrology Associates* (8) - N. Nivera; *Western Nephrology And Metabolic Bone Disease, PC* (8) - M. Anger; *South Broward Research, LLC* (8) - K. Blaze; *Rocky Mountain Institute of Clinical Research* (8) - J. Liljenquist; *Academic Medical Research Institute* (8) - M. El-Shahawy; *Veterans Administration Medical Center of Phoenix* (8) - P. Baker; *Francis M. Vazquez Roura, MD* (8) - F. Vazquez Roura; *Montgomery Kidney Specialist* (8) - R. Lopez; *South Carolina Cancer Specialists* (8) - M. Moustafa, A. Geneidy; *Natchitoches Internal Medicine* (8) - O. Barnum; *Bucyrus Internal Medicine Inc* (8) - R. Harris; *Capital Medical Clinic* (8) - H. Maldonado; *University of Arkansas for Medical Science* (8) - M. Krause; *Odyssey Research* (8) - A. Tello; *Alpha Clinical Research, LLC* (8) - J. Endsley; *VA Puget Sound Healthcare System* (7) - B. Young; *Dallas VA Medical Center* (7) - S. Banerjee, F. Kazi; *Down East Medical Associates* (7) - M. Lawrence; *Atlanta Diabetes Associates* (7) - P. Davidson; *Infosphere* (7) - D. Streja; *PharmQuest* (7) - R. Avva; *Research Institute of the Carolinas* (7) - B. Seaton; *Albany Internal Medicine* (7) - P. Donnan; *Kozinn, Marc J MD* (7) - M. Kozinn; *Eisenhower Medical Associates* (7) - P. Bradley; *Eastern Nephrology Associates* (7) - M.D. Vannorsdall, J. Hoggard; *Diabetes/Lipid Management Center* (7) - P. Rosenbilt; *Cardiology and Medicine Clinic* (7) - J. Hargrove, S. Peppers; *Pioneer Medical Group* (7) - P. Doshi; *Hanover Medical Specialists, PA* (7) - K. Kotz, P. Whitesides; *Gibbs, Hettie MD* (7) - H. Gibbs; *Padre Coast Clinical Research* (7) - J. Sandoval; *Texas Medical Research Associates Llc* (7) - P. Peters; *Gulf Coast Endocrinology* (7) - B. Lansden, M. Piracha; *Clopton Clinic* (7) - M. Wood; *CAIMED Center, Ponce School of Medicine* (7) - E. Barranco; *Clayton Medical Research* (6) - E. Heidbrier, N. Ghazal-Albar; *Methodist Hospitals of Memphis* (6) - M. Stegman; *Ochsner Health Systems* (6) - F. Husserl; *Cardiovascular Center of Sarasota* (6) - M. El-Shahawy; *The Vancouver Clinic, Inc* (6) - L. Lee; *Florida Kidney and Hypertension Care* (6) - B. Gupta; *Kaner Medical Group* (6) - D. Livingstone; *Internal Medicine Specialists, Inc.* (6) - K. Murray; *Montgomery Kidney Specialists* (6) - R. Lopez, K. Williams; *Bloomberg, Robert J MD* (6) - R. Bloomberg; *MetroHealth Medical Center* (6) - E. Ricanati; *University of Rochester, Strong Cardiology Associates* (6) - S. Reddy; *Slocum-Dickson Medical Group* (6) - D. Goodman; *Alzohaili Medical Consultants* (6) - O. Alzohaili; *Troy Internal Medicine, P.C.* (6) - N. Fraser; *Creighton Diabetes Center* (6) - M. Rendell, R. Lund; *Eastwick Medical Practice* (6) - D. Fox; *Highland Clinic* (6) - D. Persson; *MIMA Century Research* (6) - R. Vicari; *Texas Tech University Health Science Center* (6) - A. Nwosu; *Professional Clinical Research* (6) - G. Ryckman; *Mississippi Medical Research* (6) - A. Haidar; *Northeast Clinical Research Centers, Inc* (5) - N. Kopyt; *Diabetes Care and Information Center* (5) - E. Ocampo, D. Lorber; *Arcuri Clinical Research* (5) - F. Mazzotta, P. Arcuri; *Biolab Research* (5) - M. Belledonne; *Charles River Medical Associates* (5) - V. Desai; *Butler Medical Associates* (5) - D. Evanko; *IMG Healthcare* (5) - P. Mottram; *Perelman Center for Advanced Medicine* (5) - D. Cohen; *Palm Harbor Medical Associates* (5) - A. Schlaue; *Jacksonville Center for Clinical Research* (5) - M. Koren; *South Arkansas Nephrology and Hypertension* (5) - M. Kashif, K. Mahmood; *Renal Care Consultants*

(5) - G. Frem; *Advanced Medical Research, LLC* (5) - S. Finkelstein; *Commonwealth Internal Medicine & Geriatrics* (5) - V. Bakhshi; *Cardiovascular Consultants Medical Group* (5) - M. DeVane; *Preferred Primary Care Physicians of Uniontown* (5) - R. Cook; *Southern California Endocrine Center* (5) - M. Lin; *CNS Clinical Studies* (5) - H. Harris, A. Pietri; *Medical Institute of Little Company of Mary* (5) - J. Tamkin; *Arroyo Research Inc* (5) - J. Prasad; *North Chicago VA Medical Center* (5) - S. Singh; *Nephrology Hypertension Clinic, P.C.* (5) - K. Thavarajah; *Odyssey Research* (5) - S. Grubb; *Clinical Research Development Associates, LLC* (5) - D. Scott III; *Internal Medicine Associates* (5) - M. Nielsen; *Agha, Maher MD* (4) - M. Agha; *Emory University School Of Medicine* (4) - B. Khan; *Renaissance Family Practice* (4) - B. Kevish; *White Memorial Medical Center* (4) - A. Lau; *Northwest Renal Clinic Inc* (4) - M. Walczyk; *Doner, David W Jr. MD* (4) - D. Doner Jr; *Northern Colorado Research, Inc.* (4) - P. Smith; *Upstate Pharmaceutical Research* (4) - K. Pudi; *Campbell, Jeanne M MD* (4) - J. Campbell; *Scott, Robert MD* (4) - R. Scott; *Cardiovascular & Critical Care Associates, PC* (4) - M. Geller; *Prasad, Sriranga MD* (4) - S. Prasad; *Canyon Clinical Research, LLC* (4) - G. Lasala; *Southeast Texas Clinical Research* (4) - M. Castellanos; *University Hospitals* (4) - B. Efron, D. Adler; *Altru Health System* (4) - E. Johnson; *Physicians' Center for Clinical Research - Associated Internists of Ahwatukee, P.C.* (4) - E. Tokatljan; *DiGiovanna Family Care Center* (4) - M. DiGiovanna; *Sutter Gould Medical Foundation* (4) - C. Tsai; *Quality Clinical Research, Inc.* (4) - L. Zacharia; *Advanced Medical Research Institute* (4) - G. Dhillon; *Chandler and Thakur Medical Group* (4) - B. Chandler; *Southern California Clinical Research, Inc.* (4) - N. Chien; *Clinical Trials of St. Jude Heritage Medical Group* (3) - J. Gilbert; *Maxine Hamilton, MD, PA* (3) - M. Hamilton; *Metro Atlanta Kidney Specialists* (3) - S. Handelsman; *Mountain Kidney Research Inc* (3) - J. Aiello, B. Ling; *Medical University Of South Carolina* (3) - J. Fernandes; *Lewin Fagen Lown MD PC* (3) - J. Lown; *Andrawis, Nabil MD* (3) - N. Andrawis; *Tucson Clinical Research* (3) - T. Fagan, G. Lasala; *George Washington University Medical Center* (3) - S. Lew; *Red Rock Research Center* (3) - R. Prabhu; *Brigham and Women's Hospital* (3) - A. Singh; *Christie Clinic* (3) - J. Stokes; *One Heart, The Cardiology Specialists* (3) - A. Morgan; *Professional Clinical Research, Inc* (3) - W. George; *Lillestol Research, LLC* (3) - M. Lillestol; *Dr Martinez Medical Clinic* (3) - D. Martinez; *Merced Heart Associates* (3) - M. Nallasivan; *University of Rochester, School of Medicine and Dentistry* (3) - T. Rocco; *Rowan Research Inc* (3) - K. Morton; *Pentucket Medical Associates* (3) - S. Bilazarian; *Evanston Northwestern Healthcare* (3) - L. Ho; *Knoll, Herman C MD* (3) - H. Knoll; *Mirani Mamendra, MC DC* (3) - M. Mirani; *Hightop Medical Research Center* (3) - J. Fidelholtz; *Bay Area Health Clinic* (3) - D. Shrestha; *Southern California Clinical Research, Inc.* (3) - L. Wynstock; *Cody Medical Associates* (3) - R. Carlson; *Central Nebraska Medical Clinic* (3) - D. Minnick; *Louisiana Heart Center* (3) - B. Iteld; *Olathe Medical Center* (3) - K. Herron; *Spence Medical Research LLC* (3) - J. Riser; *Summit Medical Group* (3) - M. Passarello; *Internal Medicine Associates* (3) - S. Thompson; *Diabetes Research Center* (3) - J. Selam, A. Charles; *Steven Wright Nephrology Clinic* (3) - S. Wright; *Institute of Diabetes & Endocrinology* (2) - R. Eddy; *Washington University School of Medicine* (2) - D. Coyne; *Diabetes Control and Endocrinology Centers* (2) - C. Raine; *William S. Middleton Memorial VA Hospital* (2) - Y. Shenker; *Compass Medical East Bridgewater* (2) - J. Ellis; *Kaner Medical Group* (2) - M. Haider; *Southern Clinical Research & Management, Inc.* (2) - A. Carr; *Louisiana State University Health Sciences Center* (2) - T. Giles; *Medford Medical Clinic Research Department* (2) - H. Glatte; *PPS Clinical Research* (2) - P. Garrett; *Endocrine Clinic PC* (2) - J. Cohen; *Lovelace Medical Center* (2) - J. Gleeson, A. Adolphe; *Cramer and Crouse Cardiology* (2) - L. Crouse; *Women's Medical Research Group* (2) - L. Harper; *Vainer and Vainer Nephrology and*

Hypertension Consultants, Inc (2) - A. Vainer; Northwestern University, Feinberg School of Medicine (2) - M. Molitch; Lancaster Cancer Center LTD (2) - P. Casale; A Medical Corporation (2) - L. Glaser; Mid Valley Cardiology (2) - E. Lader; Washington County Hospital (2) - O. Adler; Dupage Family Medicine (2) - J. Cunnar; Nephrology Associates Research Center (2) - T. Minga; Butler Medical Associates (2) - D. Demby; Fox Valley Nephrology Partners (2) - D. Koeper; Clinical Research Center of GA (2) - S. Palmer; Texas Tech University Health Sciences Center- Division of Clinical Research (2) - M. Bakdash; Diabetes and Endocrinology (2) - N. Fishman; Advanced Healthcare (2) - R. Jain; Founders Research Corporation (2) - G. Yeoman; Family and Internal Medicine Associates (2) - D. George; Center for Rheumatology and Bone Research (2) - S. Srikanth; Medical Arts Associates (2) - A. Pareigis; Diabetes Center of the Southwest/c/o Pharmaseek (2) - G. Gollapudi; Ohio Medical Group / North Ohio Heart Center (2) - E. Gross-Sawicka; Southern California Clinical Research, Inc. (2) - P. Liu; Lexington Clinic. (2) - C. Stafford; Eastern Nephrology Associates (2) - N. Atassi; Edinger Medical Group Inc (2) - M. Sperling; University of Tennessee, Health Science Center (1) - R.B. Canada, S. Acchiardo; Physicians Research Group (1) - R. Khairi; Albert Einstein Health Care Network (1) - R. Raja; California Clinical Research Trials (1) - M. Robinson; South Taber Family Physicians (1) - M. Tso; OK Foundation for CV Research (1) - P. Adamson, R. Kipperman; Veterans Administration Medical Centers (1) - D. Lu; International Research Center (1) -A. Yataco; Arizona Center for Internal Medicine (1) - R. Fowler; Clinical Research Institute of Northern Virginia (1) - P. Narayan; New York University School of Medicine (1) - N. Thompson, L. Pillon; Carolina Clinical Research (1) - R. Montgomery, L. Rocamora; Heart and Vascular Instiute of St Petersburg (1) - R. Blanchard; Suncoast Clinical Research (1) - L. Badillo, J. Penabad; Desert Valley Medical Center (1) - C. Abarikwu; MODEL Clinical Research Inc (1) - J. Mersey; Arroyo Oaks Medical Associates (1) - F. Weil; Clinical Trials Research (1) - J. Wayne; Northport Veterans Affairs Medical Center (1) - A. Kapoor; Preferred Primary Care Physicians (1) - N. Bennett; Medstar Health (1) - M. Magee; Cardiology Consultants of Danville (1) - G. Miller; Jacksonville Heart Center (1) - M. Litt; Northern Pines Health Center (1) - M. Hewitt; University of California at Los Angeles (UCLA) (1) - D. Heber; Janick Medical Group (1) - J. Janick; Heart Group (1) - M. Wigger; Illinois Center for Clinical Research (1) - F. Apantaku; Linder Center (1) - D. Kereiakes; Amarillo Heart Clinical Research Institute Inc. (1) - E. Rivera; Rush-Presbyterian-St. Luke's Medical Center (1) - G. Schaer; Tallahassee Endocrine Associates (1) - T. Sherraden; St. Alexius Medical Center dba Clinical Research Services (1) - E. Dunnigan, C. Sharp, E. Sundberg; Diabetes Center of the Southwest (1) - B. Patel; Raval, Pramond MD PC (1) - P. Raval; Primary Healthcare Associates (1) - S. Barnes; Texas Research Center, LLP (1) - A. McCain; Wadhwa, Arvind MD (1) - A. Wadhwa; Vienna Family Medicine (1) - K. Lee; Heart Clinic of Arkansas (1) - R. Hundley; Kaner Medical Group (1) - S. Parekh; St Vincent Staten Island Hospital (1) - S. Grossman; University of Wisconsin, Medical School (1) - J. Morledge; OMNI Family Medical Center (1) - A. Nunyakpe; University of Missouri, Columbia (1) - M. Misra; NuLife Clinical Research Inc. (1) - P. Pan; Preferred Primary Care Physicians (1) - J. Moreci; Dedicated Clinical Research (1) - C. Anderson; Horizons West Medical Group (1) - A. Magana; Charles River Medical Associates (1) - S. Kramer, H. Kirshenbaum

TREAT Dosing Algorithm

Subjects in both arms received investigational product (darbepoetin alfa or placebo) by subcutaneous injection. All dose assignments were managed using an interactive voice response system (IVRS) which utilized a pre-specified dosing algorithm based on the subject's hemoglobin and rate of rise.

Darbepoetin alfa Arm

This algorithm was designed to titrate the dose of the darbepoetin alfa group to maintain hemoglobin levels at approximately 13 g/dL, taking into account both rate of rise and stability of hemoglobin levels.

Initially, study drug was administered every two weeks but once a hemoglobin level between 12.0 and 13.5 g/dL was maintained with no dosage adjustments, the frequency of drug administration was extended to monthly with the dosage doubled. To maintain blinding, the IVRS assigned comparable changes to placebo patients (Appendix C).

The initial dose of darbepoetin alfa for each subject in the treatment arm was 0.75 µg/kg. Doses were adjusted as necessary to maintain a hemoglobin of 13 g/dL. Dose increases did not occur more frequently than once monthly. The protocol specified a maximum monthly dose of 600 µg. Doses were initially administered once every 2 weeks, however, once a subject had achieved 2 consecutive hemoglobin levels within 12.0 – 13.5 g/dL, with no change in dose, the frequency of administration was extended to once monthly, with the initial once monthly dose of darbepoetin alfa equal to twice the previous every 2-week dose. Subjects receiving the lowest dose of darbepoetin alfa every 2 weeks who required a dose decrease, also had their dosing interval extended to monthly. If a subject was unable to maintain the hemoglobin target while on the monthly dosing regimen, the subject was reverted back to the once every 2 week dosing frequency.

Placebo Arm

To prevent unblinding, an IVRS algorithm ensured that the dosing frequency schedule changes occurring in the darbepoetin alfa arm were mirrored in the placebo arm. If at any time a placebo subject's hemoglobin fell below 9.0 g/dL, rescue therapy with darbepoetin alfa was initiated with a single dose of 0.45 µg/kg. Rescue therapy continued to be assigned per a predefined dosing algorithm until the subject's hemoglobin reached ≥ 9.0 g/dL, at which time placebo injections were resumed.

Darbepoetin alfa Dosing Algorithm

Hb (g/dL)	Hb rate of rise (g/dL/2 weeks)	Dose Adjustment
< 12.5	< 0.5	Increase to next higher dose
	≥ 0.5 - < 1.0	Maintain dose
	≥ 1.0	Decrease to next lower dose
12.5 - < 13.5	< 0.5	Maintain dose
	≥ 0.5 - < 1.0	Maintain dose
	≥ 1.0	Decrease to next lower dose
13.5-14.0	Any	Decrease to next lower dose
> 14.0	Any	Administer placebo until Hb value is below 13.0, then resume darbepoetin alfa at next lower dose

Rescue Therapy Dosing Algorithm

Hb (g/dL)	Hb rate of rise (g/dL/2 weeks)	Dose Adjustment
< 9.0	< 0.5	Initiate or increase to next higher dose
< 9.0	≥ 0.5, but < 1.0	Maintain dose
< 9.0	≥ 1.0	Decrease to next lower dose
≥ 9.0	Any	Resume placebo administration

TREAT Endpoint Definitions

I. DEATH CLASSIFICATION

The Clinical Endpoints Committee (CEC) at Brigham and Women's Hospital adjudicated all reports of death to determine the most likely *cause* of death. All deaths were assumed Cardiovascular in nature unless a Non-Cardiovascular cause could be clearly shown. Death was classified in the following categories:

A. Cardiovascular Death

Fatal Myocardial Infarction:

Death that occurred a) within 14 days after a documented myocardial infarction in which there is no conclusive evidence to another cause of death or in subjects who are being treated for myocardial infarction and die as a result of complications of a myocardial infarction, b) with autopsy evidence of a recent infarct with no other conclusive evidence of another cause of death, or c) abruptly with suggestive criteria for an infarct but does not meet the strict definition of a myocardial infarction. The suggestive criteria required clinical presentation of chest pain AND either ECG changes indicative of an acute injury, abnormal markers without evolutionary changes, or other evidence of wall motion abnormality.

Pump/Heart Failure:

Death that occurred within the context of clinically worsening symptoms and/or signs of heart failure without evidence of another cause of death unless directly related to an acute MI occurring within 14 days.

Sudden Death:

Death that occurred unexpectedly in an otherwise stable subject. Sudden Death was further sub-classified as "witnessed" or "Last seen \geq 1 hr and $<$ 24 hours".

Presumed Sudden Death:

Death that occurred unexpectedly in an otherwise stable subject in which the subject was last seen \geq 24 hours before death and circumstances are suggestive of sudden death.

Presumed Cardiovascular Death:

Death that occurred when the subject was last seen $>$ 24 hours before death and presumed cardiovascular in nature.

Stroke:

Death that occurred after a documented stroke.

Pulmonary Embolism:

Death that occurred after and as a result of a pulmonary embolism.

Cardiovascular Procedure-Related:

Death that occurred during a cardiovascular procedure or as a result of later complications related to the procedure within 15 days.

Other Cardiovascular:

Death that occurred due to a fully documented cardiovascular cause not included above.

Unknown:

All other cases of death, in the absence of a clearly defined non-cardiovascular or specific cardiovascular cause were classified as Unknown.

B. Non-Cardiovascular Death:

Deaths were considered non-cardiovascular only if an unequivocal and documented non-cardiovascular cause could be established. Examples of Non-CV sub classifications included: Pulmonary, Malignancy, Infection, Hepatobiliary, Gastrointestinal, Renal, Procedural, Accidental, Suicide, and Other.

II. NON-FATAL ENDPOINT DEFINITIONS

A. Presentation with Congestive Heart Failure

Presentation with congestive heart failure was adjudicated if subjects presented to healthcare provider or emergency department with an unplanned exacerbation of heart failure defined as follows:

Symptoms consistent with heart failure, including at least one of the following:

- a) Increasing dyspnea on exertion
- b) New orthopnea
- c) Paroxysmal nocturnal dyspnea
- d) Increasing fatigue with decreasing exercise tolerance

and

Two or more objective signs of heart failure:

- a) Pulmonary edema
- b) Elevated jugular venous pressure
- c) Radiologic signs of heart failure
- d) Rales

requiring treatment with

- a) intravenous diuretic therapy
- or**
- b) inotropic therapy
- or**
- c) intravenous vasodilation therapy

B. Myocardial Infarction and Hospitalization for Acute Myocardial Ischemia

The CEC adjudicated the worst-case event per calendar day for these 2 events.

Hospitalization for myocardial ischemia required a hospital presentation specifically for an acute coronary syndrome with a documented change in calendar day prior to discharge. In addition, there must have been ischemic symptoms (i.e., pain, dyspnea, pressure) at rest or accelerated ischemic symptoms, either of which lasted ≥ 10 minutes that the investigator determined was secondary to ischemia with either a) ischemic ECG changes (i.e., ≥ 0.5 mm transient ST segment depression in two contiguous limb or precordial leads, ≥ 1 mm transient ST elevation of two contiguous leads or ST depression in V1 or V2, ≥ 2 mm transient T wave change in two or more contiguous leads, ≥ 0.5 mm change as compared to most recent ECG or during the previous stable phase) or b) intermediate cardiac marker elevation suggestive of myocardial injury (i.e., $>$ upper limit of normal but not sufficient for MI criteria or troponin in the 'suggestive' (middle) range for necrosis).

Acute myocardial infarction did not require a hospitalization specifically for the event. A marker elevation was required. Non-procedural MI required any combination of markers where Troponin was ≥ 2 times

upper limit normal, CKMB \geq 2 times upper limit normal, or serial changes of CK \geq 2 times upper limit normal consistent with MI *only* in absence of troponin and CKMB. Post-percutaneous coronary intervention MI required any combination of markers where Troponin was \geq 3 times upper limit normal, CKMB \geq 3 times upper limit normal, or serial changes of CK \geq 3 times upper limit normal consistent with MI *only* in absence of troponin and CKMB. Post-Coronary artery bypass graft surgery MI required CKMB \geq 5 times upper limit normal, or either new pathological Q waves that were persistent at discharge or documentation of new wall motion abnormality (other than septal) *only* in absence of markers. In addition, *non-procedural MI* events required either ischemic ECG changes or ischemic symptoms as detailed above.

Recurrent MI: In order to make the determination whether there was evidence for a reinfarction, the subject must have been clinically stable and symptom free for at least 12 hours since the previous event and had to meet the MI definition above. In addition, the appropriate 'rise and fall' of cardiac markers was required.

C. Stroke

Stroke was defined as a focal neurological deficit (resulting from a vascular cause involving the central nervous system) of sudden onset that was not reversible within 24 hours (including death) and which was not due to a readily identifiable cause (i.e., brain tumor, trauma). If there was an imaging study done (or other clearly documented supporting source documentation), stroke was further differentiated as hemorrhagic, non-hemorrhagic, or unknown (when there was no clinical, radiological, or other substantial evidence to document either a hemorrhagic or non-hemorrhagic stroke but a stroke was believed to have occurred).

D. Revascularization

The occurrence of a coronary revascularization procedure (CABG, PCI) or peripheral revascularization procedure (Carotid, Peripheral, Renal arteries, Abdominal aortic aneurysm) met this endpoint.

E. Resuscitated Sudden Death (RSD)

A subject that experienced sudden death or cardiac arrest, with or without premonitory heart failure or myocardial infarction, and was resuscitated by cardioversion, defibrillation or cardiopulmonary resuscitation met this endpoint. This definition excluded known transient losses of consciousness such as seizure or vasovagal episodes that did not reflect significant cardiac dysfunction.

F. End Stage Renal Disease (ESRD)

Decrement in the subject's kidney function to a level at which either dialysis or kidney transplantation were required to sustain life meeting one of the following: a) Underwent >30 days of dialysis therapy, b) received a kidney transplant, c) a physician recommended renal replacement therapy (dialysis and/or transplant) and the subject refused therapy, or d) began dialysis and expired <30 days later.

Additional Statistical Methods

We compared baseline characteristics, follow-up measures, and clinical outcomes on an intent-to-treat basis according to randomization assignment. Categorical variables are summarized with frequencies and percentages, and continuous measures using medians and interquartile ranges. Pearson's chi-square test was used for dichotomous and unordered categorical data and the Wilcoxon rank sum test for ordered categorical and continuous variables. Hemoglobin, vital signs and adverse events are analyzed for subjects who received at least one dose of study drug (8 subjects assigned darbepoetin alfa and 7 assigned placebo received none). Hemoglobin and blood pressure over time are summarized using area under the curve methods.

TREAT Consort Diagram

	Overall n (%)	Darbopoetin Alfa n (%)	Placebo n (%)
Screened	8008		
 ---> Screen Failures	3961		
 ---> Randomized	4047		
 ---> Removed from database due to violation of Good Clinical Practice *	9	4	5
 ---> Included in Study Report	4038 (100)	2012 (100)	2026 (100)
 ---> Completed follow-up through 28Mar09	2716 (67)	1349 (67)	1367 (67)
 ---> Completed follow-up on treatment ..	1848 (46)	931 (46)	917 (45)
 ---> Early treatment termination	868 (21)	418 (21)	450 (22)
 ---> Death+ prior to 28Mar09	807 (20)	412 (20)	395 (19)
 ---> Discontinued follow-up prior to 28Mar09 #.	515 (13)	251 (12)	264 (13)
 ---> Known alive on 28Mar09	198 (5)	98 (5)	100 (5)
 ---> Vital status unknown on 28Mar09	317 (8)	153 (8)	164 (8)

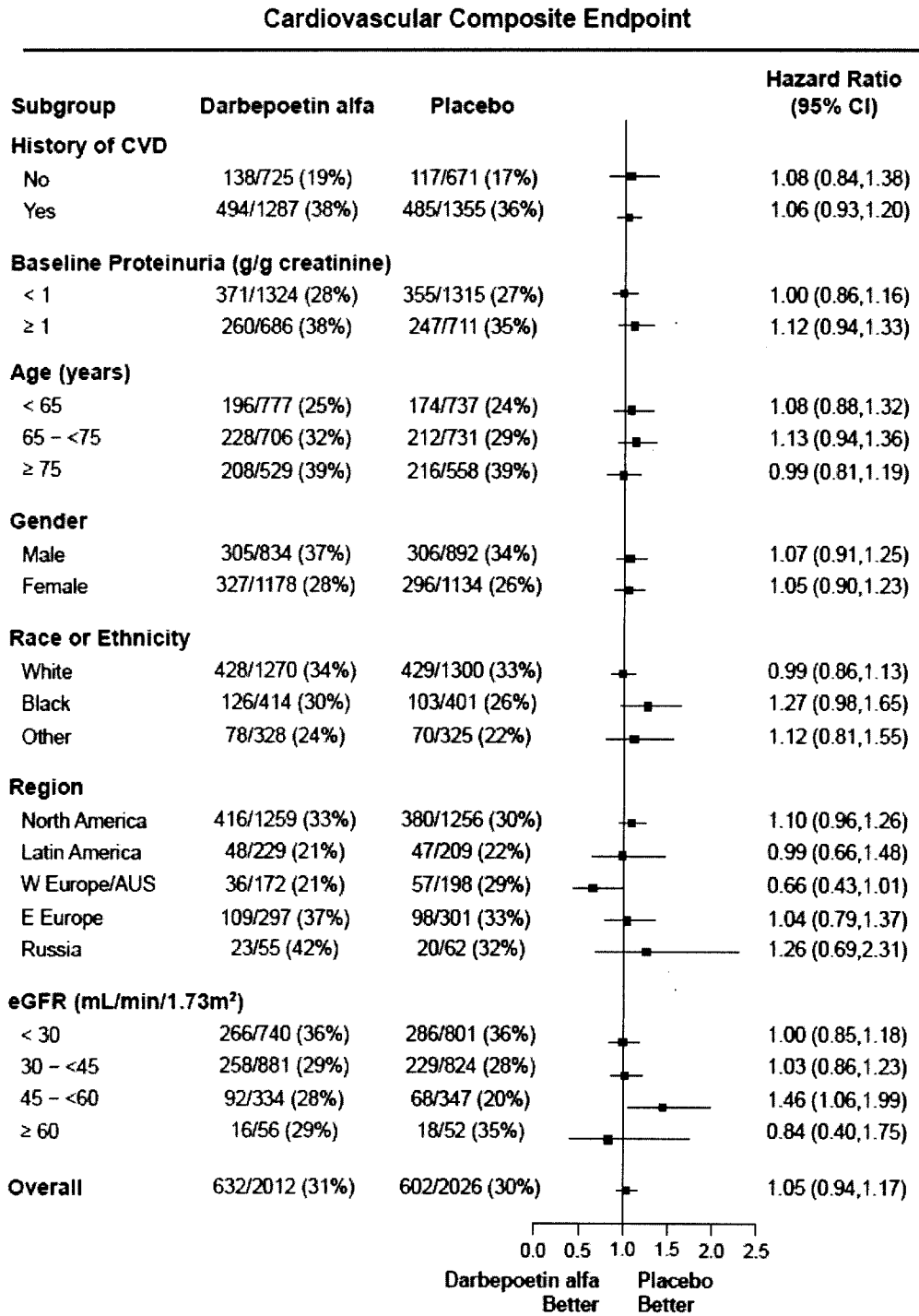
* All subjects enrolled at one clinical site in Argentina (n=3) and one site in Romania (n=6).

+ An additional 17 patients are known to have died within 30 days of 28Mar09, 7 in the darbopoetin group and 10 in the placebo group.

Of the 515 subjects who discontinued follow-up prior to 28Mar09, 68 (34 in each treatment group) had previously experienced a nonfatal primary cardiovascular composite event.

Subgroups

Hazard ratios for the primary cardiovascular composite endpoint in prespecified subgroups. Subgroups of history of CVD and baseline proteinuria (g/g creatinine) are derived from clinical database



Summary of Adverse Events

	Darbepoetin alfa (N=2004) n (%)	Placebo (N=2019) n (%)
All Adverse Events (AEs)	1880 (93.8)	1878 (93.0)
Serious Adverse Events	1235 (61.6)	1219 (60.4)
Pre-specified Events of Interest ^a	863 (43.1)	825 (40.9)
Hypertension	491 (24.5)	446 (22.1)
Myocardial infarction ^b	128 (6.4)	108 (5.3)
Cardiac failure ^b	292 (14.6)	330 (16.3)
Cerebrovascular disorders ^b	161 (8.0)	102 (5.1)
Hemorrhagic cerebrovascular disorders	89 (4.4)	49 (2.4)
Ischemic cerebrovascular disorders	150 (7.5)	96 (4.8)
Convulsions	9 (0.4)	4 (0.2)
All thromboembolic events	219 (10.9)	170 (8.4)
Venous thromboembolic events	41 (2.0)	23 (1.1)
Arterial thromboembolic events	178 (8.9)	144 (7.1)
Vascular access thrombosis	4 (0.2)	3 (0.1)
Antibody-mediated pure red cell aplasia	0 (0)	0 (0)
Malignancy-related Adverse Events ^c	139 (6.9)	130 (6.4)

N=The number of patients received at least one dose of investigational product. Percentages based on N.

^a The events of interest (EOI) were pre-specified in the Statistical Analysis Plan using preferred terms (PT) identified by Standard MedDRA Queries (SMQ) prior to database lock (MedDRA Version 11.1). Each EOI is defined by a specified set of PTs, however a given PT may be categorized into more than one EOI.

^b EOI categories may overlap with adjudicated clinical outcomes. AEs were reported by the investigator and were not adjudicated by the clinical endpoint committee, while the clinical outcomes were adjudicated in a masked manner based on pre-specified criteria.

^c Malignancy was not a pre-specified EOI. The category of malignancy-related AEs was defined using PT identified by SMQ for Malignancy.