SUPPLEMENTAL MATERIAL

CREDENCE Collaborative Network

**Steering Committee:** Vlado Perkovic (Chair), Kenneth W. Mahaffey (co-chair), Rajiv Agarwal, George Bakris, Barry M. Brenner, Christopher P. Cannon, David M. Charytan, Dick de Zeeuw, Tom Greene, Meg J. Jardine, Hiddo J.L. Heerspink, Adeera Levin, Gary Meininger (Sponsor), Bruce Neal, Carol Pollock, David C. Wheeler, Hong Zhang, Bernard Zinman

**Independent Data Monitoring Committee:** Darren K. McGuire (chair), Rury Holman, Philip Home, Dan Scharfstein, Patrick Parfrey

**Endpoint Adjudication Committee:** Rajiv Agarwal (chair), Kenneth W. Mahaffey (co-chair), Shahnaz Shahinfar, Phyllis August, Tara Chang, Arjun D. Sinha, James Januzzi, Daniel Kolansky, John Amerena, Graham Hillis, Philip Gorelick, Brett Kissela, Scott Kasner, Richard Lindley, Greg Fulcher

**Cardiovascular Adjudication Committee:** Kenneth W. Mahaffey, James Januzzi, Daniel Kolansky, John Amerena, Graham Hillis

**Renal Adjudication Committee:** Rajiv Agarwal, Shahnaz Shahinfar, Phyllis August, Tara Chang, Arjun D. Sinha

**Stroke Adjudication Committee:** Richard Lindley, Philip Gorelick, Brett Kissela, Scott Kasner
Safety Adjudication

Fracture Adjudication: Souhila Ounadjela, Karina Hufert, Gabriele von Ingersleben (Bioclinica)

Diabetic Ketoacidosis Adjudication: Jason Gaglia, Ronald Harris, Margo Hudson, Alexander Turchin (Baim)

Pancreatitis Adjudication: Adam Cheifetz, Sunil Sheth, Joseph Feuerstein (Baim)

Renal Cell Carcinoma Adjudication: Samuel Cohen

Regional Lead Investigators: Meg Jardine (Global Scientific Lead), Hiddo J.L. Heerspink (Europe Regional Scientific Lead), David M. Charytan (Americas Regional Scientific Lead), Nicole Li and Inna Kolesnyk (Asia Pacific Regional Scientific Leads)

National Lead Investigators: Diego Aizenberg (Argentina and Chile), Roberto Pecoits-Filho (Brazil), Adeera Levin and David Cherney (Canada), Gregorio Obrador (Mexico, Colombia, and Guatemala), Glenn Chertow and Tara Chang (United States), Carmel Hawley (Australia and New Zealand), Linong Ji and Hong Zhang (China), Takashi Wada (Japan), Vivekanand Jha (India), Soo Kun Lim (Malaysia), Mary Anne Lim-Abraham and Florence Santos (Philippines), Dong-Wan Chae (South Korea), Shang-Jyh Hwang (Taiwan), Evgueni Vazelov (Bulgaria), Ivan Rychlík (Czech Republic and Slovakia), Samy Hadjadji (France), Vera Krane (Germany), László Rosivall (Hungary), Luca De Nicola (Italy), Alexander Dreal (Russia), Michał Nowicki (Poland), Adalbert Schiller (Romania), Larry Distiller (South Africa), Jose L Górriz (Spain), Mykola Kolesnyk (Ukraine), David C. Wheeler (United Kingdom)
Operational Teams

**Janssen**: Fran Morren, Svetlana Goykhman, Caryl David, Lori Yost, Holly Wang

**George Clinical**: Manthi Hettiarchchi, Ramesh Thimmaiah, Deepak Koppolu, Sini George, Manuela Schmidt

**IQVIA**: Jelena Ignjatovic, Lincoln Chapin, Kim Travis, Martine Destree, Vivek Sood, Laura Coffee, Kati De Brouwer, Viktor Zaviriukha, Agnieszka Starzec, Masahiro Koizumi, Grace Lin, Evaly Chen, Peggy Lin, Chen Leia, Debbie Mascaro, Anabella Amigo, Ana Limos

**Baim Institute for Clinical Research**: Ingrid Abrahamsen, Sara Jaffer
Participating Countries and Collaborating Investigators

Argentina: Rodolfo Andres Ahuad Guerrero, Diego Aizenberg, Juan Pablo Albisu, Andres Alvarisqueta, Ines Bartolacci, Mario Alberto Berli, Anselmo Bordonava, Pedro Calella, Maria Cecilia Cantero, Luis Rodolfo Cartasegna, Esteban Cercos, Gabriela Cecilia Coloma, Hugo Colombo, Victor Commendatore, Jesus Cuadrado, Carlos Alberto Cuneo, Ana Maria Cusumano, Walter Guillermo Douthat, Ricardo Dario Dran, Eduardo Farias, Maria Florencia Fernandez, Hernan Finkelstein, Guillermo Fragale, Jose Osvaldo Fretes, Nestor Horacio Garcia, Anibal Gastaldi, Elizabeth Gelersztein, Jorge Archibaldo Glenny, Joaquin Pablo Gonzalez, Patricia del Carmen Gonzalez Colaso, Claudia Goycoa, Gustavo Cristian Greloni, Adrian Guinsburg, Sonia Hermida, Luis Isaias Juncos, Maria Isabel Klyver, Florencia Kraft, Fernando Krynski, Paulina Virginia Lanchiotti, Ricardo Alfonso Leon de la Fuente, Nora Marchetta, Pablo Mele, Silvia Nicolai, Pablo Antonio Novoa, Silvia Ines Orio, Fabian Otreras, Alejandra Oviedo, Pablo Raffaele, Jorge Hector Resk, Lucas Rista, Nelson Rodriguez Papini, Jorgelina Sala, Juan Carlos Santos, Lilia Beatriz Schiavi, Horacio Sessa, Tomas Smith Casabella, Maria Rosa Ulla, Maria Valdez, Augusto Vallejos, Adriana Villarino, Virginia Esther Visco, Alfredo Wassermann, Cesar Javier Zaidman;

Australia: Ngai Wah Cheung, Carolyn Droste, Ian Fraser, David Johnson, Peak Mann Mah, Kathy Nicholls, David Packham, Joseph Proietto, Anthony Roberts, Simon Roger, Venessa Tsang;

Brazil: Roberto Abrão Raduan, Fernando Augusto Alves da Costa, Celso Amodeo, Luiz Alberto Andreotti Turatti, Rachel Bregman, Fernanda Cristina Camelo Sanches, Luis Henrique Canani, Antônio Roberto Chacra, João Lindolfo Cunha Borges, Sérgio Alberto Cunha Vêncio, Roberto Jorge da Silva Franco, Domingos d’Avila, Evandro de Souza Portes, Pedro de Souza, Luciane Mônica Deboni, Fadlo Fraige Filho, Bruno Geloneze Neto, Marcus Gomes, Suely Keiko Kohara,
Elizete Keitel, Jose Francisco Kerr Saraiva, Hugo Roberto Kurtz Lisboa, Fabiana Loss de Carvalho Contieri, Rosângela Milagres, Renan Montenegro Junior, Claudia Moreira de Brito, Miguel Nasser Hissa, Ângela Regina Nazario Sabbag, Irene Noronha, Daniel Panarotto, Roberto Pecoits Filho, Márcio Antônio Pereira, Wladmir Saporito, Antonio Scafuto Scotton, Tiago Schuch, Roberto Simões de Almeida, Cássio Slombo Ramos, João Soares Felício, Fernando Thomé, Jean Carlo Tibes Hachmann, Sérgio Yamada, Cesar Yoiti Hayashida, Tarissa Beatrice Zanata Petry, Maria Teresa Zanella; **Bulgaria**: Viktoria Andreeva, Angelina Angelova, Stefan Dimitrov, Veselka Genadieva, Gabriela Genova-Hristova, Kiril Hristozov, Zdravko Kamenov, Atanas Koundurdjiev, Lachezar Lozanov, Viktor Margaritov, Boyan Nonchev, Rangel Rangelov, Alexander Shinkov, Margarita Temelkova, Ekaterina Velichkova, Andrian Yakov; **Canada**: Naresh Aggarwal, Ronnie Aronson, Harpreet Bajaj, David Cherney, Guy Chouinard, James Conway, Serge Cournoyer, Gerald DaRoza, Sacha De Serres, François Dubé, Ronald Goldenberg, Anil Gupta, Milan Gupta, Sam Henein, Hasnain Khandwala, Lawrence Leiter, Adeera Levin, François Madore, Alan McMahon, Norman Muirhead, Vincent Pichette, Remi Rabasa-Lhoret, Andrew Steele, Navdeep Tangri, Ali Torshizi, Vincent Woo, Nadia Zalunardo; **Chile**: María Alicia Fernández Montenegro, Juan Gonzalo Godoy Jorquera, Marcelo Medina Fariña, Victor Saavedra Gajardo, Margarita Vejar; **China**: Nan Chen, Qinkai Chen, Shenglian Gan, Yaozhong Kong, Detian Li, Wenge Li, Xuemei Li, Hongli Lin, Jian Liu, Weiping Lu, Hong Mao, Yan Ren, Weihong Song, Jiao Sun, Lin Sun, Ping Tu, Guixia Wang, Jinkui Yang, Aiping Yin, Xueqing Yu, Minghui Zhao, Hongguang Zheng; **Colombia**: Jose Luis Accini Mendoza, Edgar Arcos, Jorge Avendano, Jorge Ernesto Andres Diaz Ruiz, Luis Hernando Garcia Ortiz, Alexander Gonzalez, Eric Hernandez Triana, Juan Diego Higuera, Natalia Malaver, Dora Inés Molina de Salazar, Ricardo Rosero, Monica Alexandra
Terront Lozano, Luis Valderrama Cometa, Alex Valenzuela, Ruben Dario Vargas Alonso, Ivan Villegas, Hernan Yupanqui; **Czech Republic**: Dagmar Bartaskova, Petr Barton, Jana Belobradkova, Lenka Dohnalova, Tomas Drasnar, Richard Ferkl, Katarina Halciakova, Vera Klokocnikova, Richard Kovar, Jiri Lastuvka, Martin Lukac, Satu Pesickova, Karel Peterka, Jiri Pumprla, Ivan Rychlik, Frantisek Saudek, Vladimir Tesar, Martin Valis, Pavel Weiner, Stanislav Zemek; **France**: Eric Alamartine, Sophie Borot, Bertrand Cariou, Bertrand Dussol, Jean-Pierre Fauvel, Pierre Gourdy, Alexandre Klein, Yannick Le Meur, Alfred Penfornis, Ronan Roussel, Pierre-Jean Saulnier, Eric Thervet, Philippe Zaoui; **Germany**: Volker Burst, Markus Faghih, Grit Faulmann, Hermann Haller, Reinhold Jerwan-Keim, Stephan Maxeiner, Björn Paschen, Georg Plassmann, Ludger Rose; **Guatemala**: Ronaldo Arturo Gonzalez Orellana, Franklin Paul Haase, Juan Pablo Moreira Diaz, Luis Alberto Ramirez Roca, Jose Antonio Sánchez Arenales, José Vicente Sanchez Polo, Erick Turcios Juarez; **Hungary**: Gyongyi Csecsei, Botond Csiky, Peter Danos, Laszlo Deak, Mihaly Dudas, Eleonora Harcsa, Katalin Keltai, Sandor Keresztesi, Krisztian Kiss, Laszlo Konyves, Lajos Major, Margit Mileder, Marta Molnar, Janos Mucsi, Tamas Oroszlan, Ivan Ory, Gyorgy Paragh, Eva Peterfai, Gizella Petro, Katalin Revesz, Robert Takacs, Sandor Vangel, Szilard Vasas, Marianna Zsom; **India**: Oomman Abraham, Raju Sree Bhushan, Dewan Deepak, Fernando M. Edwin, Natarajan Gopalakrishnan, Noble Gracious, Alva Hansraj, Dinesh Jain, C.B. Keshavamurthy, Dinesh Khullar, Sahay Manisha, Jayameena Peringat, Narayan Prasad, Rao K. Satyanarayana, Reddy Sreedhar, Melemadathil Sreelatha, Bhimavarapu Sudhakar, Ramesh Chandra Vyasam; **Italy**: Riccardo Bonadonna, Pietro Castellino, Antonio Ceriello, Luca Chiovato, Salvatore De Cosmo, Luca De Nicola, Giuseppe Derosa, Alberto Di Carlo, Graziano Di Cianni, Giovanni Frascà, Giorgio Fuiano, Giovanni Gambaro, Giacomo Garibotto, Carlo Giorda,
Fabio Malberti, Marcora Mandreoli, Edoardo Mannucci, Emanuela Orsi, Piermarco Piatti, Domenico Santoro, Ferdinando Carlo Sasso, Gaetano Serviddio, Andrea Stella, Roberto Trevisan, Anna Maria Veronelli, Luca Zanoli; **Japan:** Hitoshi Akiyama, Hiromi Aoki, Akimichi Asano, Tadashi Itsuka, Shizuo Kajiyama, Susumu Kashine, Toshio Kawada, Takamoto Kodera, Hiroshi Kono, Kazunori Koyama, Yasuro Kumeda, Shozo Miyachi, Kazuyuki Mizuyama, Tetsuji Niiya, Hiroko Oishi, Satoshi Ota, Terue Sakakibara, Masahiko Takai, Osamu Tomonaga, Mitsuru Tsujimoto, Takashi Wada, Masakiyo Wakasugi, Yasushi Wakida, Takayuki Watanabe, Masayo Yamada, Kazuhiro Yanagida, Toshihiko Yanase, Wataru Yumita; **Lithuania:** Egle Gaupsiene, Dalia Kozloviene, Antanas Navickas, Egle Urbanaviciene; **Malaysia:** Rohana Abdul Ghani, Khalid Abdul Kadir, Norsiah Ali, Mohd Daud Che Yusof, Chye Lee Gan, Mastura Ismail, Wei Yen Kong, Swee Win Lam, Li Yuan Lee, Soo Kun Lim, Chek Loong Loh, Anita Bhajan Manocha, Kee Sing Ng, Nik Nur Fatnoon Nik Ahmad, Vanassa Ratnasingam, Saiful Shahrizal Bin Shudim, Paranthaman Vengadasalam; **Mexico:** Luis David Abraira Munoz, Melchor Alpizar Salazar, Juan Baas Cruz, Mario Burgos Soto, Jose Chevaile Ramos, Alfredo Chew Wong, Jose Ricardo Correa Rotter, Tonatiu Diaz Escalante, Favio Edmund Enriquez Sosa, Fernando Flores Lozano, Luis Fernando Flota Cervera, Paul Frenk Baron, Cecilia Garcia Ballesteros, Jose David Gomez Rangel, Luis Enrique Herrera Jimenez, Sergio Saul Irizar Santana, Fernando Jimenez Flores, Hugo Laviada Molina, Rosa Isela Luna Ceballos, Belia Martin del Campo Blanco, Guadalupe Morales Franco, Oscar Tarsicio Moreno Loza, Cynthia Mustieles Rocha, Gregorio Obrador Vera, Ricardo Orozco Castellanos, Juan Peralta Calcaneo, Miguel Angel Reyes Rosano, Hiromi Rodriguez Pattzi, Juan Rosas Guzman, Isabel Erika Rucker Joerg, Sandra Berenice Saavedra Sanchez, Jose Hector Sanchez Mijangos, Pablo Serrano Sanson, Juan Alfredo Tamayo y Orozco, Eloisa Tellez Chavez,
Alejandro Valdes Cepeda, Luis Venegas Carrillo, Juan Villagordoa Mesa, Rolando Zamarripa Escobedo; **New Zealand:** John Baker, Paul Noonan, Russell Scott, Robert Walker, Edward Watson, Michael Williams, Simon Young; **Philippines:** Zaynab Abejuela, Jeimeen Agra, Grace Aquitania, Clodoaido Caringal, Rhea Severina Comia, Lalaine Delos Santos, Olivert Gomez, Cecilia Jimeno, Florence Santos, Gerry Tan, Marsha Tolentino, Christy Yao, Yvette Ethel Yap, Ma. Dovie Lallaine Ygpuara; **Poland:** Renata Bijata-Bronisz, Lucyna Hotlos, Andrzej Januszewicz, Barbara Kaczmarek, Anna Kaminska, Lech Lazuka, Andrzej Madej, Stanislaw Mazur, Dorota Mlodawska-Choluj, Michal Nowicki, Grazyna Orlowska-Kowalik, Grazyna Popenda, Barbara Rewerska, Dariusz Sowinski; **Romania:** Liliana Monica Angelescu, Veronica Anghel, Rodica-Ioana Avram, Mihaela-Magdalena Busegeanu, Adriana Cif, Dana Cosma, Carmen Crisan, Luiza Despina Demian, Ioana Emilia Ferariu, Ildiko Halmagyi, Nicolae Hancu, Mircea Munteanu, Doru Negru, Adriana Gabriela Onaca, Ligia Petrica, Amorin Remus Popa, Aurelian-Emil Ranetti, Cristian Serafinceanu, Cristina Toarba; **Russia:** Alina Agafyina, Olga Barbarash, Olga Barysheva, Daniil Chizhov, Vladimir Dobronravov, Alexander Dreval, Irina Glinkina, Elena Grineva, Vladimir Khirmanov, Elena Kolmakova, Tatiana Koroleva, Liudmila Kvitkova, Viacheslav Marasaev, Ashot Mkrtumyan, Tatiana Morugova, Galina Nagibovich, Oleg Nagibovich, Sergei Nedogoda, Irina Osipova, Tatiana Raskina, Yulia Samoylova, Olga Sazonova, Minara Shamkhalova, Elena Shutemova, Yuriy Shwartz, Oleg Uriasyev, Sergey Vorobyev, Anna Zateyshchikova, Dmitry Zateyshshikov, Tatyana Zykova; **Serbia:** Slobadan Antic, Miodrag Djordjevic, Aleksandra Kendereski, Katarina Lalic, Nebojsa Lalic, Vesna Popovic-Radinovic; **Slovakia:** Jana Babikova, Olga Benusova, Ingrid Buganova, Jan Culak, Andrej Dzupina, Jana Dzuponova, Peter Fulop, Adriana Ilavska, Emil Martinka, Zuzana Ochodnicka, Daniel Pella, Iveta Smatanova; **South Africa:**
Fayzal Ahmed, Aysha Badat, Johannes Breedt, Lawrence Distiller, Vimladhevi Govender, Ravendran Govender, Mukesh Joshi, Jaco Jurgens, Gulam Latiff, Landman Lombard, Mohamed Mookadam, Nomangesi Ngcakani, Hendrik Nortje, Helena Oosthuizen, Larisha Pillay-Ramaya, Hans Prozesky, Jeevren Reddy, Paul Rheeder, Mary Seeber; South Korea: Dong-Wan Chae, Young Min Cho, In-Kyung Jeong, Sin Gon Kim, Yeong Hoon Kim, Hyuk-Sang Kwon, Min Jeong Kwon, Byung-Wan Lee, JungEun Lee, Moon-Kyu Lee, Moon-Suk Nam, Kook-Hwan Oh, Cheol-Young Park, Sun-Hee Park, Kun Ho Yoon; Spain: Pere Alvarez Garcia, Luis Asmarats Mercadal, Clara Barrios, Fernando Cereto Castro, Secundino Cigarran Guldris, Marta Dominguez Lopez, Jesus Egido de los Rios, Gema Fernandez Fresnedo, Antonio Galan Serrano, Isabel Garcia, Francisco Javier Gonzalez Martinez, Jose Esteban Jodar Gimeno, Manuel Lopez Mendoza, Tamara Malek Marin, Cristobal Morales Portillo, Maria Antonia Munar Vila, Manuel Muñoz Torres, Javier Nieto Iglesias, Jonay Pantoja Perez, Merce Perez Vera, Jose Maria Portoles Perez, Maria Angustias Quesada Simón, Rafael Simo Canonge, Alfonso Soto Gonzalez, Manel Terns Riera, Francisco Jose Tinahones Madueno, Mercedes Velo Plaza; Taiwan: Chwen-Tzuei Chang, Lee-Ming Chuang, Te-Lin Hsia, Chang-Hsun Hsieh, Shang-Jyh Hwang, Chih-Ching Lin, Yung-Chuan Lu, Wayne H-H Sheu; Ukraine: Olga Barna, Svitolana D. Bilyk, Volodymyr Botsyurko, Iryna Dudar, Ivan Fushtey, Olga Godlevska, Oleksandr Golovchenko, Olga Gyrina, Anatoliy Kazmirchuk, Mykola Kolesnyk, Iuliia Komisarenko, Oleksii Korzh, Nonna Kravchun, Oleg Legun, Borys Mankovskyy, Liliya Martynyuk, Yuriy Mostovoy, Nataliia Pashkovska, Larysa Pererva, Tetyana Pertseva, Oleksandr Samoylov, Ivan Smirnov, Yevgeniya Svyschchenko, Halyna Tomashkevych, Ivan Topchii, Nadiya Tryshchuk, Vira Tseluyko, Vadym Vizir, Maryna Vlasenko, Tetiana Zlova, Liliia Zub; United Arab Emirates: Salah Abusnana, Mohamed Railey; United
**Kingdom:** Kamal Abouglila, Paul Ainsworth, Zishan Ali, Vijayaraman Arutchelvam, Maria Barnard, Srikanth Bellary, Emyr Davies, Mark Davies, Simon Davies, Alison Dawson, Mohsen El Kossi, Patrick English, Donald Fraser, Luigi Gnudi, Anthony Gunstone, Timothy Hall, Wasim Hanif, Alan Jackson, Andrew Johnson, Franklin Joseph, Singhan Krishnan, Mick Kumwenda, Iain MacDougall, Paul Nixon, Joseph O'Hare, Sam Philip, Shenaz Ramtoola, Manish Saxena, Davesh Sennik, Godwin Simon, Baldev Singh, Jeffrey Stephens, Anna Strzelecka, Rehan Symonds, Wayne Turner, Mona Wahba, John Wakeling, David Wheeler, Peter Winocour; **United States:** Joseph Abdallah, Raied Abdullah, Matthew Abramowitz, Idalia Acosta, Joseph Aiello, Laura Akright, Ayim Akyea-Djamson, Rajendran Alappan, Radica Alicic, Amer Al-Karadsheh, Dale Crawford Allison, Carlos Arauz-Pacheco, Shahabul Arfeen, Ahmed Arif, Moogali Arvind, Naveen Atray, Ahmed Awad, George Bakris, Peggy Barnhill, Elizabeth Barranco, Carlos Barrera, Matthew Beacom, Venkata Behara, Diogo Belo, Rhonda Bentley-Lewis, Ramon Berenguer, Lidia Bermudez, Marializa Bernardo, Mihaela Biscoveanu, Cynthia Bowman-Stroud, Donald Brandon, Osvaldo Brusco, Robert Busch, Yamil Canaan, Alicia Chilito, Tom Christensen, Cynthia Cristiano, Elena Christofides, Caroucel Chuateco, Kenneth Cohen, Robert Cohen, Debbie Cohen-Stein, Charles Cook, Daniel Coyne, Nizar Daboul, Riad Darwish, Adarsh Daswani, Kenneth Deck, Cyrus Desouza, Devasmita Dev, Monika Dhillon, Sohan Dua, Frank Eder, Ana Maria Elosegui, Mohamed El-Shahawy, John Ervin, Alberto Esquenazi, John Evans, Steven Fishbane, Juan Frias, Eugenia Galindo-Ramos, Claude Galphin, Adline Ghazi, Enrique Gonzalez, David Gorson, Anupama Gowda, Barbara Greco, Stephen Grubb, Rakesh Gulati, Jamal Hammoud, Stuart Handelsman, Israel Hartman, Kenneth Hershon, Daniel Hiser, George Hon, Radu Jacob, Maria Jaime, Aamir Jamal, Charles Kaupke, Gerald Keightley, Elizabeth Kern, Rakhi Khanna, Zeid
Khitan, Sun Kim, Nelson Kopyt, Csaba Kovesdy, Gopal Krishna, Jeffrey (Jay) Kropp, Amrendra Kumar, Jayant Kumar, Neil Kumar, Jorge Kusnir, Wendy Lane, Mary Lawrence, Lawrence Lehrner, John Lentz, Dennis Levinson, Derek Lewis, Kenneth Liss, Andreas Maddux, Hiralal Maheshwari, Sreedhar Mandayam, Isam Marar, Bhasker Mehta, John Middleton, Jorge Mordujovich, Ramon Moreda, Moustafa Moustafa, Samuel Mujica Trenche, Mohanram Narayanan, Javier Narvarte, Tareq Nassar, George Newman, Brian Nichol, Philip Nicol, Josier Nisnisan, A. Kaldun Nossuli, Chamberlain Obialo, Sarah Olelewe, Michael Oliver, Andrew O'Shaughnessy, John Padron, Rohit Pankhaniya, Reginald Parker, Devesh Patel, Gnyandev Patel, Nina Patel, Humberto Pavon, Armando Perez, Carlos Perez, Alan Perlman, Karlton Pettis, Walter Pharr, Andrea Phillips, Raman Purighalla, Luis Quesada-Suarez, Rajiv Ranjan, Sanjeev Rastogi, Jakkidi Reddy, Marc Rendell, Lisa Rich, Michael Robinson, Hector Rodriguez, Sylvia Rosas, Fadi Saba, Rallabhandi Sankaram, Ravi Sarin, Robert Schreiman, David Scott, Mohamed Sekkarie, John Sensenbrenner, Muhammad Shakeel, Michael Shanik, Sylvia Shaw, Stephen Smith, Richard Solomon, Amy Sprague, Leslie Spry, Pusadee Suchinda, Senan Sultan, Prasanth Surampudi, Sherry Sussman, Anjanette Tan, Antonio Terrelonge, Michael Thompson, Fernando Trespalacios, Bruce Trippe, Pilar Trueba, Marcel Twahirwa, John Updegrove, Peter Van Buren, Mark Vannorsdall, Freemu Varghese, Pedro Velasquez-Meyer, Sailaja Ventrapragada, Goga Vukotic, Khurram Wadud, Mark Warren, Henry Watson, Ronald Watts, Daniel Weiner, James Welker, Jean Welsh, Shelley Williams, Michelle Zaniewski-Singh.
**Inclusion and Exclusion Criteria**

**Inclusion Criteria at Screening Visit**

1. Man or woman ≥30 years old with a clinical diagnosis of type 2 diabetes mellitus (T2DM).
2. Glycated hemoglobin (HbA1c) ≥6.5% to ≤12.0%, (≥6.5% to ≤10.5% in Germany).
3. Estimated glomerular filtration rate (eGFR) ≥30 to <90 mL/min/1.73 m$^2$ (as determined using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation).

   Note: An overall global target ratio for randomized cohort of approximately 60%:40% for CKD Stage 3 (i.e., eGFR ≥30 to <60 mL/min/1.73 m$^2$; first category):CKD Stage 2 (i.e., eGFR ≥60 to <90 mL/min/1.73 m$^2$; second category) will be monitored centrally. In an effort to limit exposure to investigational product and to ensure sufficient experiences in subjects with Stage 3 CKD, entry of subjects with Stage 2 CKD (i.e., eGFR ≥60 to <90 mL/min/1.73 m$^2$) may be restricted on a regional and/or site basis should the ratio drift substantially off target over the course of the recruitment period.
4. Urinary albumin:creatinine ratio (UACR) >300 mg/g to ≤5000 mg/g (>33.9 mg/mmol to ≤565.6 mg/mmol).
5. All subjects must be on a stable maximum tolerated labeled daily dose of angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) for at least 4 weeks prior to randomization.

   Note: A maximum tolerated labeled daily dose of an ACEi or ARB is defined as the maximum approved labeled dose for diabetic nephropathy (for agents with an approved indication for diabetic nephropathy in patients with T2DM, i.e., losartan and irbesartan).
or the maximum approved dose for hypertension (for agents without an approved indication for diabetic nephropathy), unless side effects or adverse events limit the use of the maximum approved dose. For subjects who are not on a maximum labeled daily dose of an ACEi or ARB, investigators will be required to document why a higher dose should not be used.

6. Women must be:
   - postmenopausal, defined as
     - >45 years of age with amenorrhea for at least 18 months, or
     - >45 years of age with amenorrhea for at least 6 months and <18 months and a serum follicle stimulating hormone (FSH) level >40 IU/L, or
   - surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal occlusion [which includes tubal ligation procedures as consistent with local regulations]), or otherwise be incapable of pregnancy, or
   - heterosexually active and practicing a highly effective method of birth control, including hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method (e.g., condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel), or male partner sterilization, and consistent with local regulations regarding use of birth control methods for subjects participating in clinical studies, for the duration of their participation in the study, or
   - not heterosexually active.
Note: Subjects who are not heterosexually active at screening must agree to utilize a highly effective method of birth control if they become heterosexually active during their participation in the study.

7. Women of childbearing potential (i.e., those subjects who do not meet the postmenopausal definition above), regardless of age, must have a negative urine pregnancy test at baseline (Day 1) and at screening if required by local regulations. Note: A serum pregnancy test is acceptable in lieu of a urine pregnancy test if required by local regulations.

8. Willing and able to adhere to the prohibitions and restrictions specified in this protocol.

9. Subjects must have signed an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study. Each subject must also sign a separate informed consent form if he or she agrees to provide an optional DNA sample for research (where local regulations permit). Refusal to give consent for the optional DNA research sample does not exclude a subject from participation in the study.

Inclusion Criterion for Randomization

10. Subjects must have ≥80% compliance (by pill count) with single-blind placebo.

Exclusion Criteria

Potential subjects who meet any of the following criteria will be excluded from participating in the study:
Diabetes-related/Metabolic

1. History of diabetic ketoacidosis or type 1 diabetes mellitus (T1DM).

2. History of hereditary glucose-galactose malabsorption or primary renal glucosuria.

Renal/Cardiovascular

3. Known medical history or clinical evidence suggesting nondiabetic renal disease.

4. Renal disease that required treatment with immunosuppressive therapy or a history of chronic dialysis or renal transplant.

Note: Subjects with a history of treated childhood renal disease, without sequelae, may participate.

5. Uncontrolled hypertension (systolic blood pressure [BP] ≥180 and/or diastolic BP ≥100 mmHg) by Week –2.

Note: Subjects not fulfilling BP criteria at the initial screening visit may have their BP-lowering medication regimen adjusted, followed by re-evaluation up to the Week –2 run-in period (the ACEi or ARB regimen must be stable for at least 4 weeks before Day 1 to be eligible).

6. Blood potassium level >5.5 mmol/L during screening.

Note: Subjects in whom hyperkalemia was associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs), β-blockers, or mineralocorticoid receptor antagonists (MRAs; e.g., spironolactone or eplerenone), who have been withdrawn from these drugs, and in whom usage of these drugs is not indicated in the view of the treating physician, may be included in the study.
7. Myocardial infarction, unstable angina, revascularization procedure (e.g., stent or bypass graft surgery), or cerebrovascular accident within 12 weeks before randomization, or a revascularization procedure is planned during the trial.

8. Current or history of heart failure of New York Heart Association (NYHA) class IV cardiac disease (The Criteria Committee of the NYHA).

9. Electrocardiogram (ECG) findings within 12 weeks before randomization that would require urgent diagnostic evaluation or intervention (e.g., new clinically important arrhythmia or conduction disturbance).

**Gastrointestinal**

10. Known significant liver disease (e.g., acute hepatitis, chronic active hepatitis, cirrhosis).

**Laboratory**

11. Alanine aminotransferase (ALT) levels >2.0 times the upper limit of normal (ULN) or total bilirubin >1.5 times the ULN, unless in the opinion of the investigator and as agreed upon by the sponsor’s medical officer, the findings are consistent with Gilbert’s disease.

**Other Conditions**

12. History of malignancy within 5 years before screening (exceptions: squamous and basal cell carcinomas of the skin and carcinoma of the cervix in situ, or a malignancy that in the opinion of the investigator, with concurrence with the sponsor’s medical monitor, is considered cured with minimal risk of recurrence).

13. History of human immunodeficiency virus (HIV) antibody positive.

14. Major surgery within 12 weeks before randomization, or has not fully recovered from surgery.
15. Any condition that in the opinion of the investigator or sponsor’s medical monitor would make participation not in the best interest of the subject, or could prevent, limit, or confound the protocol-specified assessments.

16. History of atraumatic amputation within past 12 months of screening, or an active skin ulcer, osteomyelitis, gangrene, or critical ischemia of the lower extremity within 6 months of screening (added May 5, 2016).

**Medications/Therapies**

17. Combination use of an ACEi and ARB.

18. Use of an MRA or a direct renin inhibitor (DRI).

Note: If deemed clinically appropriate at the discretion of the investigator, subjects may be removed from therapy with an MRA or DRI during screening. Subjects who are off therapy with an MRA or DRI for at least 8 weeks prior to randomization may be considered eligible for enrollment.

19. Current use of a sodium glucose co-transporter 2 (SGLT2) inhibitor (within 12 weeks prior to randomization).

20. Current participation in another canagliflozin study or previously exposed to canagliflozin in a prior canagliflozin study.

21. Known allergies, hypersensitivity, or intolerance to canagliflozin or its excipients.

22. Received an active investigational drug (including vaccines) other than a placebo agent, or used an investigational medical device within 12 weeks before Day 1/baseline.

**General**

23. Pregnant or breast-feeding or planning to become pregnant or breast-feed during the study.
24. Employees of the investigator or study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center, as well as family members of the employees or the investigator.

Note: Investigators should ensure that all study enrollment criteria have been met and determine that the subject has not had any interval change in clinical status since the time of the initial screening visit. Before randomization, subjects whose clinical status changes after screening such that they now meet an exclusion criterion should be excluded from participation.
Safety Analyses

- **Adverse events (AEs):** All AEs will be collected and coded using the *Medical Dictionary for Regulatory Activities (MedDRA)* from randomization until 30 days after the last date of blinded study medication.

- **AEs of interest:** All malignancies, renal cell carcinoma, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (e.g., angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious AEs of hepatic injury, nephrotoxicity/acute kidney injury, venous thromboembolic events, fractures, diabetic ketoacidosis (and related AEs including ketoacidosis, metabolic acidosis, or acidosis), amputation, and pregnancy.

- **Hypoglycemia:** All episodes of hypoglycemia (both symptomatic and asymptomatic) are recorded on a dedicated hypoglycemia electronic case report form (eCRF).

- **Safety laboratory tests:** Chemistry, hematology, urinalysis.

- **Physical examination:** Pulse, blood pressure, weight.
### Supplemental Figure 1. Effects of canagliflozin versus placebo on safety outcomes in the secondary and primary prevention cohorts.

| Event                        | Canagliflozin | Placebo | Hazard ratio (95% CI) | Intervention Failure |
|------------------------------|---------------|---------|-----------------------|----------------------|
| **All adverse events**       |               |         |                       |                      |
| Primary                      | 86(1088)      | 31(1081) | 2.8                   | 0.08 (0.05-0.13)     |
| Secondary                    | 300(1102)     | 126(1101) | 2.4                   | 0.04 (0.02-0.07)     |
| Total                        | 386(1089)     | 157(1081) | 2.4                   | 0.05 (0.03-0.08)     |
| **All serious adverse events** |              |         |                       |                      |
| Primary                      | 207(1088)     | 30(1081) | 7.0                   | 0.07 (0.04-0.13)     |
| Secondary                    | 945(1102)     | 166(1101) | 5.8                   | 0.06 (0.04-0.09)     |
| Total                        | 1152(1089)    | 266(1081) | 5.8                   | 0.06 (0.04-0.09)     |
| **Serious adverse events related to study drug** | | | | |
| Primary                      | 241(1088)     | 20(1081) | 12.0                  | 1.11 (0.76-1.61)     |
| Secondary                    | 936(1102)     | 64(1101)  | 14.8                  | 1.31 (0.97-1.75)     |
| Total                        | 1177(1089)    | 84(1081)  | 14.8                  | 1.31 (0.97-1.75)     |
| **Fracture**                 | 217(1088)     | 26(1081)  | 8.5                   | 1.06 (0.74-1.57)     |
| **Cancer**                   |               |         |                       |                      |
| Need oral co-therapy         | Primary       | 10(1085) | 0.0                    | 0.1                  |
| Secondary                    | 41(1112)      | 0.0      | 0.1                   |                      |
| Total                        | 51(1217)      | 0.0      | 0.1                   |                      |
| **Breath**                   | Primary       | 5(405)   | 0.7                    |                      |
| Secondary                    | 20(405)       | 0.7      |                      |                      |
| Total                        | 25(405)       | 0.7      |                      |                      |
| **Bladder**                  | Primary       | 11(530)  | 1.2                    |                      |
| Secondary                    | 16(530)       | 1.2      |                      |                      |
| Total                        | 27(530)       | 1.2      |                      |                      |
| **Acute pancreatitis**       | Primary       | 4(530)   | 1.0                    |                      |
| Secondary                    | 11(530)       | 0.9      |                      |                      |
| Total                        | 15(530)       | 0.9      |                      |                      |
| **Hypertension**             | Primary       | 7(2005)  | 3.3                    | 0.05 (0.33-1.26)     |
| Secondary                    | 30(2005)      | 11.6     | 0.03 (0.16-0.72)      |
| Total                        | 37(2005)      | 11.6     | 0.03 (0.16-0.72)      |
| **Acute kidney injury**      | Primary       | 5(2005)  | 12.5                   | 0.09 (0.43-0.21)     |
| Secondary                    | 16(2005)      | 12.5     | 0.09 (0.43-0.21)      |
| Total                        | 21(2005)      | 12.5     | 0.09 (0.43-0.21)      |
| **Urinary tract infection**  | Primary       | 13(2005) | 4.0                    | 1.05 (0.59-2.00)     |
| Secondary                    | 17(2005)      | 4.0      | 1.05 (0.59-2.00)      |
| Total                        | 20(2005)      | 4.0      | 1.05 (0.59-2.00)      |
| **Male genital mycotic infection** | Primary | 6 (263) | 1.6                    | 8.79 (1.14-64.68)    |
| Secondary                    | 18(263)       | 1.6      | 8.79 (1.14-64.68)     |
| Female genital mycotic infection | Primary       | 6 (263) | 1.6                    | 8.79 (1.14-64.68)    |
| Secondary                    | 18(263)       | 1.6      | 8.79 (1.14-64.68)     |
| **Hypertrophic obliterative endarteritis** | Primary | 13 (1483) | 5.9                        | 0.09 (0.03-0.24)     |
| Secondary                    | 23(1483)      | 5.9      | 0.09 (0.03-0.24)      |
| Total                        | 36(1483)      | 5.9      | 0.09 (0.03-0.24)      |
| **Hypertrophic obliterative endarteritis (including acute kidney injury)** | Primary | 14(1483) | 6.0                        | 0.09 (0.03-0.24)     |
| Secondary                    | 24(1483)      | 6.0      | 0.09 (0.03-0.24)      |
| Total                        | 38(1483)      | 6.0      | 0.09 (0.03-0.24)      |

CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities.

*Diamonds represent the result of a single analysis of the full cohort. The numbers for amputation, fracture, and cancer were based on the on-study analysis set, while the other safety endpoints were based on the on-treatment analysis set.*
The analyses for fracture, renal cell carcinoma, acute pancreatitis, and diabetic ketoacidosis were based on confirmed and adjudicated results.

Hazard ratios and 95% CIs were calculated for outcomes with >10 events.

Includes female participants only.

Adverse events of hyperkalemia were spontaneously reported by the investigator. The summary counts provided for the adverse event of hyperkalemia include the MedDRA preferred terms of “hyperkalemia” and “blood potassium increased.”

All potential ketone-related events were adjudicated for diabetic ketoacidosis by an independent adjudication committee based on clinical presentation and predefined biochemical parameters.