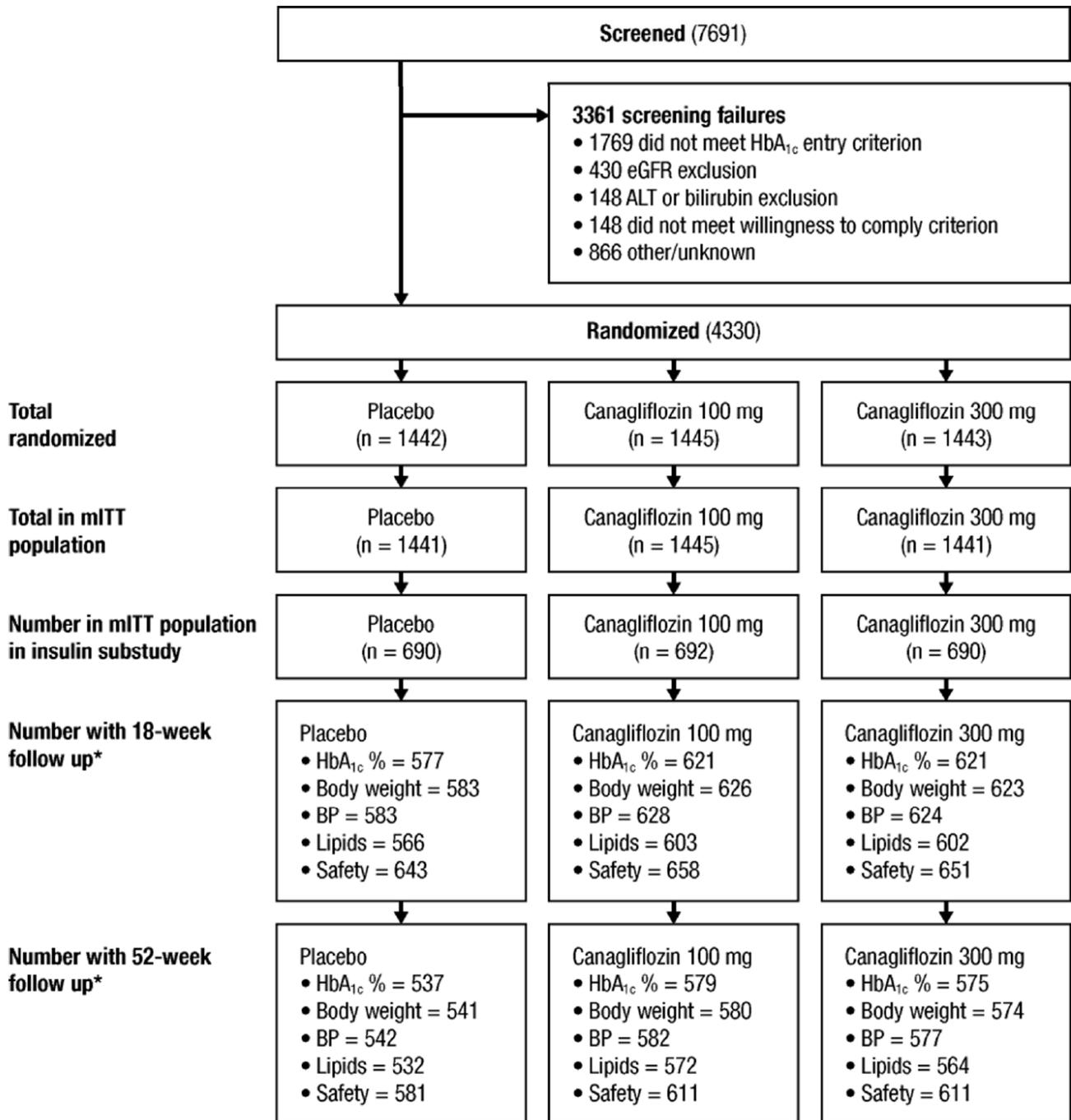


SUPPLEMENTARY DATA

Supplementary Figure 1. Flowchart.

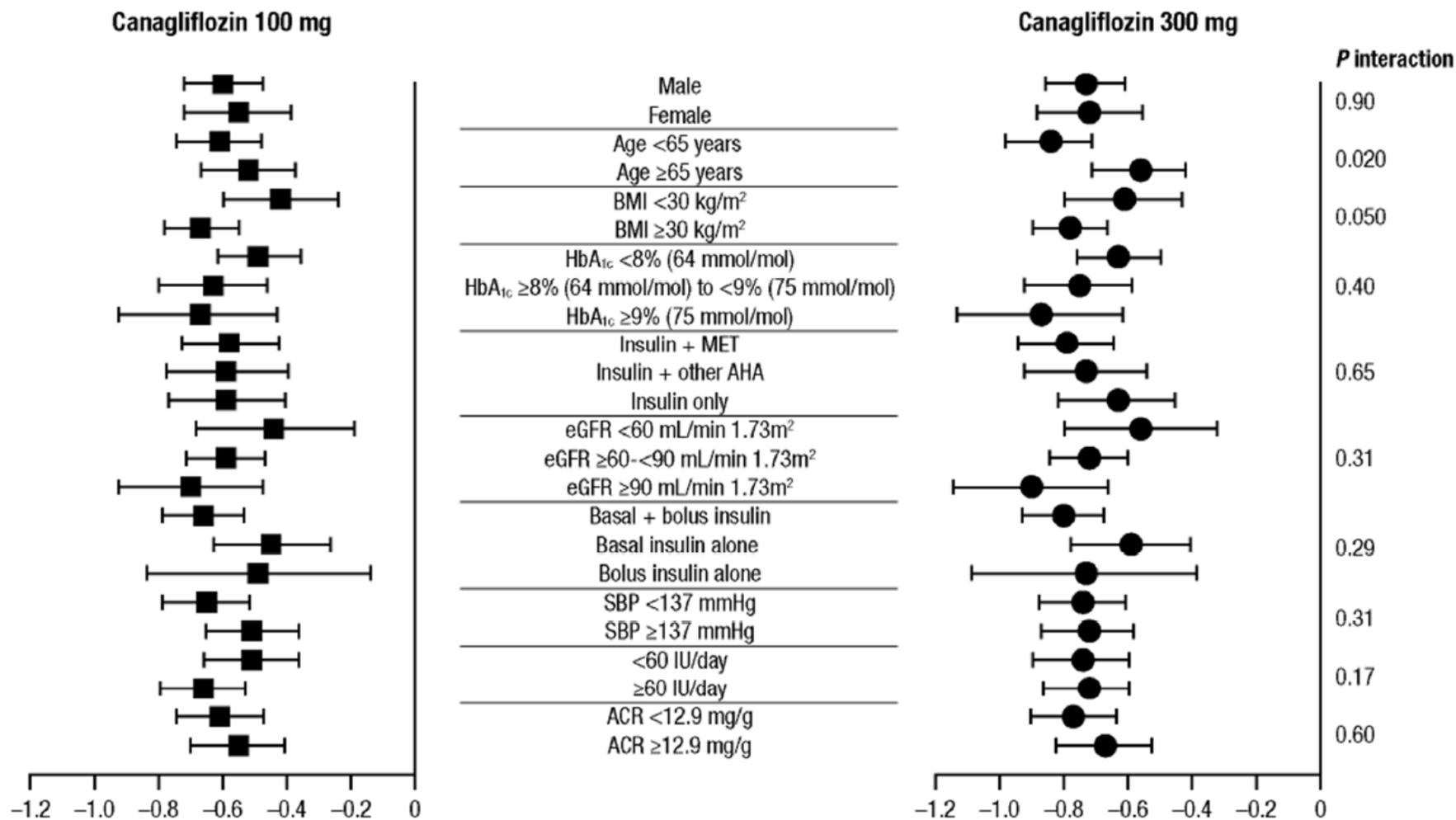


eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; mITT, modified intent-to-treat; BP, blood pressure.

*Efficacy follow-up data corresponds to the observed number of patients with laboratory data at the respective visit whereas safety follow-up data corresponds to the number of patients with site contact (clinic or telephone) at the respective visit.

SUPPLEMENTARY DATA

Supplementary Figure 2. Effects of each dose of canagliflozin compared to placebo on HbA_{1c} in patient subgroups at 52 weeks.



BMI, body mass index; MET, metformin; AHA, antihyperglycemic agent; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; ACR, albumin/creatinine ratio.

SUPPLEMENTARY DATA

Supplementary Table 1. Effects of Each Dose of Canagliflozin Compared to Placebo on Primary, Secondary, and Other Efficacy Outcomes at 18 Weeks Regardless of the Need for Rescue Therapy

	18 weeks	
	Difference (95% CI) Canagliflozin 100 mg versus placebo (n = 674 vs 668)*	Difference (95% CI) Canagliflozin 300 mg versus placebo (n = 671 vs 668)*
HbA _{1c} [†]		
%	-0.61 (-0.69, -0.53)	-0.72 (-0.80, -0.65)
mmol/mol	-6.7 (-7.5, -5.8)	-7.9 (-8.7, -7.1)
% change in body weight [†]	-2.0 (-2.3, -1.7)	-2.5 (-2.8, -2.2)
FPG (mmol/L) [†]	-1.2 (-1.4, -0.9) [‡]	-1.5 (-1.8, -1.3)
SBP (mmHg)	-2.2 (-3.6, -0.9)	-4.2 (-5.6, -2.9)
DBP (mmHg)	-0.9 (-1.7, -0.1)	-1.7 (-2.5, -0.9)
Proportion (%) HbA _{1c} <7.0% [†]	11.2 (7.4, 15.0)	17.4 (13.4, 21.4)
% change in HDL cholesterol	1.1 (-0.7, 2.9)	4.5 (2.7, 6.3)
% change in triglycerides	-1.7 (-6.0, 2.6)	-3.7 (-8.0, 0.6)
% change in LDL cholesterol	4.6 (-1.6, 10.7)	5.3 (-0.9, 11.4)
% change in total cholesterol	0.7 (-1.2, 2.5)	2.7 (0.9, 4.6)
% change in LDL:HDL cholesterol ratio	3.0 (-3.3, 9.2)	0.7 (-5.6, 6.9)
% change in non-HDL cholesterol	0.4 (-2.1, 3.0)	2.1 (-0.5, 4.6)

CI, confidence interval; FPG, fasting plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein.

*Exact n for the primary outcome; for patients with missing data, the last observation was carried forward (LOCF).

[†]Indicates endpoints that were prespecified for hypothesis testing at Week 18.

[‡]*P* <0.001 versus placebo for all prespecified hypotheses.

SUPPLEMENTARY DATA

Supplementary Table 2. Effects of Each Dose of Canagliflozin Compared to Placebo on Primary, Secondary, and Other Efficacy Outcomes at 18 and 52 Weeks in Patients Using Any Dose of Insulin (>0 IU/day)

	18 weeks		52 weeks	
	Difference (95% CI) Canagliflozin 100 mg versus placebo (n = 693 vs 671)*	Difference (95% CI) Canagliflozin 300 mg versus placebo (n = 688 vs 671)*	Difference (95% CI) Canagliflozin 100 mg versus placebo (n = 710 vs 706)*	Difference (95% CI) Canagliflozin 300 mg versus placebo (n = 702 vs 706)*
HbA _{1c} [†]				
%	-0.62 (-0.70, -0.54)	-0.73 (-0.81, -0.65)	-0.59 (-0.68, -0.49)	-0.74 (-0.84, -0.65)
mmol/mol	-6.8 (-7.7, -5.9)	-8.0 (-8.9, -7.1)	-6.4 (-7.4, -5.4)	-8.1 (-9.2, -7.1)
% change in body weight [†]	-1.9 (-2.2, -1.6)	-2.4 (-2.7, -2.1)	-2.7 (-3.2, -2.3)	-3.5 (-4.0, -3.1)
FPG (mmol/L) [†]	-1.19 (-1.44, -0.93)	-1.60 (-1.86, -1.35)	-1.15 (-1.41, -0.888)	-1.49 (-1.76, -1.23)
SBP (mmHg)	-2.54 (-3.86, -1.22)	-4.28 (-5.61, -2.95)	-3.28 (-4.66, -1.90)	-6.38 (-7.77, -4.99)
DBP (mmHg)	-1.1 (-1.9, -0.3)	-1.8 (-2.6, -1.0)	-1.2 (-2.0, -0.3)	-2.5 (-3.3, -1.6)
Proportion (%) HbA _{1c} <7.0% [†]	11.6 (7.9, 15.3)	17.4 (13.4, 21.4)	12.6 (8.7, 16.6)	18.0 (13.9, 22.1)
% change in HDL cholesterol	1.1 (-0.8, 2.9)	4.7 (2.8, 6.5)	2.3 (0.5, 4.0)	5.0 (3.3, 6.7)
% change in triglycerides	-1.7 (-6.0, 2.7)	-2.9 (-7.3, 1.4)	-1.5 (-6.3, 3.3)	-5.6 (-10.4, -0.8)
% change in LDL cholesterol [‡]	4.8 (-1.4, 10.9)	5.0 (-1.2, 11.2)	2.8 (-2.5, 8.0)	6.6 (1.3, 11.9)
% change in total cholesterol	0.7 (-1.2, 2.5)	2.9 (1.1, 4.8)	1.3 (-0.7, 3.4)	3.1 (1.1, 5.2)
% change in LDL:HDL cholesterol ratio [‡]	3.3 (-2.9, 9.5)	0.5 (-5.7, 6.6)	0.6 (-4.9, 6.0)	0.7 (-4.8, 6.2)
% change in non-HDL cholesterol	0.5 (-2.1, 3.0)	2.2 (-0.3, 4.8)	1.3 (-1.7, 4.3)	2.6 (-0.4, 5.6)

CI, confidence interval; FPG, fasting plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein.

*Exact n for the primary outcome; for patients with missing data, the last observation was carried forward (LOCF).

[†]Indicates endpoints that were prespecified for hypothesis testing at Week 18.

[‡]Outlying data from 2 subjects were excluded at Week 52; differences (95% CI) versus placebo for canagliflozin 100 and 300 mg with outliers included: LDL-C, 15.1% (-0.5, 30.7) and 7.4% (-8.7, 22.7), respectively; and LDL-C/HDL-C, 10.1% (-2.7, 22.9) and 0.8% (-12.1, 13.7), respectively.

SUPPLEMENTARY DATA

Supplementary Table 3. Criteria for the institution of glycemic rescue therapy during initial 18-week period

During the first 18-weeks of follow-up glycemic rescue criteria were applied. After Week 18, investigators are free to determine participants' glycemic goals and the need for adjustments in the glucose lowering drug regimen. From Day 1 to Week 18, the criteria for starting glycemic rescue therapy were based on an FPG value exceeding the glucose cut-points shown in the table below. Subjects were counselled to contact the site if their self-monitored blood glucose levels consistently exceeded these values. A fasting plasma glucose measurement (i.e. venous blood collection) was then done to determine eligibility for initiation of glycemic rescue therapy.

Rescue Criteria Through Week 18

Time point	Glucose
After Day 1 through Week 6	>270 mg/dL (15 mmol/L)
After Week 6 through Week 12	>240 mg/dL (13.3 mmol/L)
After Week 12 through Week 18	>200 mg/dL (11.1 mmol/L)

Glycemic rescue therapy was determined by the investigator: either up-titration of current medications or the stepwise addition of non-insulin antihyperglycemic agent(s) and then insulin therapies. After initiation of rescue therapy, the glycemic goals were based upon standard diabetes guidance, individualized for the subject, as considered appropriate by the investigator.

SUPPLEMENTARY DATA

CANVAS collaborating sites

Argentina: Pablo Arias, Maria Rosa Ulla, Andres Alvarisqueta, Laura Maffei, Jose Osvaldo Fretes, Silvia Gorban De Lapertosa, Virginia Visco, Georgina Sposetti, Javier Farias, Eduardo Francisco Farias, Maria Cecilia Cantero, Rodolfo Feldman, Maria Carolina Ridruejo, Pedro Calella, Cesar Zaidman; **Australia:** Stephen Stranks, William Jeffries, Peak Man Mah, Richard Macissac, Alison Nankervis, Duncan Topliss, Georgia Soldatos, Richard Simpson, Murray Gerstman, David Colquhoun, Ferdinandus De Looze, Robert Moses, Michael Suranyi, Samantha Hocking, David Packham, Duncan Cooke, Karam Kostner; **Belgium:** Eric Weber, Chris Vercammen, Luc Van Gaal, Jozef Tits, Evy Vandemeulebroecke, Bart Keymeulen, Chantal Mathieu; **Canada:** Naresh Aggarwal, Dan Dattani, Francois Blouin, Richard Dumas, Sam Henein, Patrick Ma, Ali Najarali, Michael Omahony, Tracy Pella, Wilson Rodger, Daniel Shu, Vincent Woo, Brian Zidel, Lew Pliamm, Brian Ramjattan, Ronald Akhras, Jasmin Belle-Isle, Stuart Ross; **Colombia:** Juan Velasquez, Luis Orozco, Alvaro Burbano; **Czech Republic:** Alena Andresova, Miloslava Komrskova, Cyril Mucha, Tomas Brychta, Dagmar Bartaskova, Romana Urbanova, Tomas Spousta, Jana Havelkova, Tomas Sedlacek, Milan Kvapil; **Estonia:** Ülle Jakovlev, Verner Fogel, Liina Viitas, Mai Soots, Maire Lubi, Marju Past, Jelena Krasnopejeva; **Germany:** Hasan Alawi, Klaus Busch, Kerstin Tyler, Andrea Thron, Stephan Jacob, Thomas Forst, Andreas Pfützner, Ludger Rose, Thomas Segiet, Christine Kosch, Andrea Moelle; **Great Britain:** Melanie Davies, Patrick Bell, Martin Gibson, Luigi Gnudi, Frances Game, John Wilding, Stephen Atkin, Thozhukat Sathyapalan, Miles Fisher, Shenaz Ramtoola, Satyan Rajbhandari, Maurice Okane; **Hungary:** Eleonora Beke, Ferenc Poor, Karoly Nagy, Gyozo Kocsis, Tamas Oroszlan, Peter Faludi, Mihaly Gurzo; **India:** Sathyanarayana Srikanta, Mala Dharmalingam, Bala Murugan, Pramod Gandhi, Bipin Sethi, Sosale Aravind, Sharda Ardhanareeshwaran, Arpan Bhattacharyya, Ganapathi Bantwal, Vijay Viswanathan, Prasanna Kumar, Banshi Saboo, Viswanathan Mohan, Neeta Deshpande, Kirti Kumar Modi, Sindhu Joshi, Sunil Jain, Sanjay Kalya, A Unni Krishnan, Prabha Adhikari, Ajay Kumar, Chittranjan Yajnik, Matthew John, Sadasivarao Yalamanchi, Keyur Parikh, Balakrishnan Kollenccheri Puthourath, Jaideep C Menon, Sasi Kumar, Lily Rodrigues, Jugal Bihari Gupta, Pankaj Agarwal, Sandeep Kumar Gupta, Abhay Amrutlal Mutha, Shailaja Dilip Kale, Ravindra Laxman Kulkarni, Sanjay Bhatt, Kamal Sharma, Yogeesh K.S., Aniruddha Tangaonkar, Vaishali Deshmukh, Biswakesh Majumdar, Rajendran Veerappan, Deepak Namjoshi; **Israel:** Itamar Raz, Julio Weinstein, Ilana Harman Boehm, Victor Vishlitzky; **Luxembourg:** Frederic Dadoun; **Malaysia:** Rajesh P. Shah, Lai Seong Hooi, Alexander Tan, Wan Mohamad Wan Bebakar, Mafauzy Mohamed, Amir S. Khir, Norlela Sukor, Khalid Abdul Kadir; **Mexico:** Enrique Morales, Sergio Zuñiga, Melchor Alpizar, Cesar Calvo, Rolando Zamarripa, Juan Rosas, Armando Vargas; **Netherlands:** Max Nieuwdorp, Vicdan Kose, Marc Peeters, Susanne Kentgens, Irma Agous, Gloria Rojas, Wouter Van Kempen, Jacqueline Hoogendijk, Mazin Alhakim, Victor Gerdes, Karin Kaasjager, Marcel Hovens, Peter E.P. Viergever, Cees Jan Smit, Dick C.G. Basart, Wilco Spiering, Marcel K. Van Dijk-Okla, Ben P.M. Imholz, Ruud J.M. Van Leendert, Marije Ten Wolde, Peter J.H. Smak Gregoor; **New Zealand:** Russell Scott, Jeremy Krebs, John Baker, Joe Singh, Calum Young; **Norway:** Gisle Langslet, Kjetil Hoeye, Hans Olav Hoivik, Torbjorn Kjaernli, Sigbjorn Elle, Helge Istad, Knut Risberg, Andreas Tandberg, Leidulv Solnoer, Per Anton Sirnes; **Poland:** Tadeusz Derezinski, Malgorzata Arciszewska, Edward Franek, Ewa Szybowska, Dariusz Sowinski, Robert Petryka, Beata Czakanska-Dec, Grazyna Pulka, Katarzyna Jusiak, Mariusz Dabrowski, Piotr Kubalski, Malgorzata Wojciechowska, Andrzej Madej, Danuta Pupek-Musialik; **Russia:** Irina Chazova, Olga Kondrashkina, Alla Ivleva, Anatoly Kuzin, Alexander Filatov, Tatyana Gomova, Alexander Khokhlov, Sergey Vorobjev, Olga Miroljubova, Svetlana Boldueva, Olga Ershova, Marina Ballyzek, Olga Smolenskaya, Sergey S. Yakushin, Dmitry Zateyshchikov, Mikhail Arkhipov, Alexandr Kuzmenko, Ivan Maksimov, Igor Motylev, Vladimir Rafalskiy, Leonid Strongin, Tatyana Treshkur, Natalya Volkova, Olga Barbarash, Tatiana Raskina, Leonid Bartosh, Inna Nikolskaya, Elena Shutemova, Viktor Gurevich, Natalia Burova, Elena Idrisova, Denis Andreev, Boris Bart, Igor Bokarev, Lyudmila Gapon, Ivan

SUPPLEMENTARY DATA

Gordeev, Nikolai Gratsiansky, Alsu Zalevskaya, Sergey Sayganov, Oleg Solovyev, Galina Reshedko, Natalia Shilkina, Petr Chizhov, Julia Shapovalova, Alexander Sherenkov, Olga Reshetko, Vladimir Simanenkov; **Spain**: Juan Garcia Puig, Jose Saban, Jose Pascual, Luis De Teresa, Jose Dominguez, Elias Delgado, Carlos Calvo, Manuel Vida, Santiago Duran, Francisco Tinahones, Jordi Salas, Jose Miguel Gonzalez, Manuel Monreal, Marco Antonio Paz, Andreu Nubiola, Pere Alvarez; **Sweden**: Kaj Stenlöf, Pekka Koskinen, Carl-Johan Lindholm, Leif Nilsson, Ulrik Mathiesen, Katarina Berndtsson Blom, Bengt-Olov Tengmark, Kjell Larsson, Hans Jul-Nielsen, Anders Norrby; **USA**: Basil Akpunonu, Rahfa Zerikly, Claire Baker, Alan Wine, Alan Kravitz, Darlene Bartilucci, Joshua Barzilay, Christian Breton, John Buse, Richard Cherlin, Michael Cobble, Clarence Ellis, Raymond Fink, Alan Forker, Ronald Garcia, Naresh Agarwal, Priscilla Hollander, Angela House, Minh Huynh, Richard Ingebretsen, David Jack, Judith Kirstein, Ferrol Lee, Daniel Lorber, Donald Mcneil, Wendell Miers, Alex Murray, Robert Call, Stephen T. Ong, Fernando Ovalle, Robert Pearlstein, Veronica Piziak, Daniel Pomposini, David Robertson, Julio Rosenstock, Ulrich Schubart, Shaukat Shah, Rodney Stout, Mark Turner, James Wallace, Leonard Chuck, Robert Weiss, Judith White, Alan Wynne, Carol Wysham, Michael Alderman, William Crump, Bryan Pogue, Arnold Silva, Roger Guthrie, Sam Lerman, Robert Madder, Katherine Nori Janosz, Daniel Weiss, Dean Kereiakes, Ronald J Graf, Negah Rassouli, Derek Muse, Vicki Kalen, Robert Kersh, Humberto Fernandez-Miro, Richard Dobrusin, Glover Johnson, Tami Bruce; **Ukraine**: Oleksandr Larin, Svetlana Panina, Galyna Popik, Svitlana Kovalenko, Olena Voloshyna, Vera Tseluyko, Olga Gyryna, Vadim Vizir, Olga Barna, Maryna Dolzhenko, Grigoriy Ignatenko, Yuriy Mostovoy, Vadim Korpachev, Boris Mankovskiy, Mykola Vatutin