

## Supplemental Materials

### *Sites and investigators in the CANVAS trial*

**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, Peak Man Mah, 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, 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, Geza Molnar; **Colombia:** Juan Manual Arteaga, Ivonne Jarava; **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, Felix Klemens Pröpper, Andrea Thron, Stephan Jacob, Andreas Pfützner, Ludger Rose, Thomas Segiet, Christine Kosch, Andrea Moelle; **Great Britain:** Melanie Davies, Hamish Courtney, Martin Gibson, Luigi Gnudi, Frances Game, John Wilding, 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, Paramesh Shamanna, Banshi Saboo, Viswanathan Mohan, Reshma Parmaj, Kirti Kumar Modi, Sindhu Joshi, Sunil Jain, Sanjay Kalra, Arun Chankramath Somasekharan, Prabha Adhikari, Ajay Kumar, Harshada Kudalkar, Rajiv Passey, Mathew John, Sadasivarao Yalamanchi, Keyur Parikh, K.P. Rajesh, Rajesh Nair, Ajay Kumar, Sasi Kumar, Lily Rodrigues, Pawan Gangwal, Pankaj Agarwal, Sandeep Kumar Gupta, Abhay Amrutlal Mutha, Shailaja Dilip Kale, Ravindra Laxman Kulkarni, Sandip Chudasama, Kamal Sharma, Anoop Nambiar, 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; **The Netherlands:** Max Nieuwdorp, Vicdan Kose, Susanne Kentgens, Gloria Rojas, Wouter Van Kempen, Jacqueline Hoogendijk, Mazin Alhakim, Victor Gerdes, Marcel Hovens, Johan Berends, A. Woittiez, Cees Jan Smit, B. Dekkers, 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, Hans Olav Hoivik, Torbjorn Kjaernli, Sigbjorn Elle, Eric Gjertsen, Knut Risberg, Andreas Tandberg, Leidulv Solnoer, Per Anton Sirnes; **Poland:** Tadeusz Dereziński, Malgorzata Arciszewska, Edward Franek, Ewa Szyprowska, Dariusz Sowinski, Robert Petryka, Beata Czakanska-Dec, Grazyna Pulka, Katarzyna Jusiak, Mariusz Dabrowski, Piotr Kubalski, Malgorzata Wojciechowska, Andrzej Madej, Danuta Pupek-Musialik; **Russia:** Natalia Blinova, Ludmila Kondratjeva, Anatoly Kuzin, Mikhail Boyarkin, Tatyana Gomova, Alexander Khokhlov, Sergey Vorobjev, Olga Mirolyubova, 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 Vorobyeva, Denis Andreev, Boris Bart, Tatiana Khlevchuk, Lyudmila Gapon, Ivan Gordeev, Nikolai Gratsiansky, Alsu Zalevskaya, Sergey Sayganov, Oleg Solovyev, Galina Reshedko, Natalia Shilkina, Petr Chizhov, Julia Shapovalova, Alexander Sherenkov, Olga Reshetko, Vladimir Simanenkoy; **Spain:** Juan Garcia Puig, Jose Saban, Jose Pascual, Jose Dominguez, Elias Delgado, Carlos Calvo, Manuel Vida, Santiago Duran, Francisco Tinahones, Jordi Salas, Jose Miguel Gonzalez, Manuel Monreal, Armand Grau, Andreu Nubiola, Pere Alvarez; **Sweden:** Kaj Stenlöf, Pekka Koskinen, Carl-Johan Lindholm, Ulrik Mathiesen, Katarina Berndtsson Blom, Bengt-Olov Tengmark, Hans Jul-Nielsen; **Ukraine:** Oleksandr Larin, Svetlana Panina, Svitlana Kovalenko, Olena Voloshyna, Vera Tseluyko, Olga Gyrina, Vadim Vizir, Olga Barna, Maryna Dolzhenko, Yuriy Mostovoy, Vadim Korpachev, Boris Mankovskiy, Mykola Vatutin; **United States:** Charles Arena, Basil Akpunonu, Rahfa Zerikly, Claire Baker, Toby Briskin, Darlene Bartilucci, Joshua Barzilay, Christian Breton, John Buse, Richard Cherlin, Michael Cobble, Clarence Ellis, Raymond Fink, Alan Forker, Ronald Garcia, Priscilla Hollander, Angela House, Daniel Hyman, Richard Ingebretsen, David Jack, Judith Kirstein, Kerri Kissell, 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, Edmund Claxton, Emily Morawski, Alan Wynne, Carol Wysham, Michael Alderman, Walter Patton, Bryan Pogue, Arnold Silva, Roger Guthrie, Sam Lerman, Robert Madder, Wendy Miller, Daniel Weiss, Dean Kereiakes, Ronald J Graf, Negah Rassouli, James Greenwald, Hanna Abu-Nassar, Derek Muse, Vicki Kalen, Natalia Hegedosh, Richard Dobrusin, Glover Johnson, Tami Bruce, Gary Gleason.

**Supplemental Table 1.** Effects of Canagliflozin on IGFBP7 Concentrations Over Time as a Function of Albuminuria Status

	N	Geometric mean IGFBP7 at baseline	Geometric mean IGFBP7 at 1 Year	Mean fold change	Ratio of mean fold change (canagliflozin/placebo)	<i>P</i> *
<b>All patients</b>						
Placebo	930	95.1	99.0	1.04	0.98	0.11
Canagliflozin	1968	97.0	99.1	1.02		
<b>Albumin/creatinine ratio &lt;30 mg/g (normal)</b>						
Placebo	676	92.9	95.9	1.03	0.99	0.53
Canagliflozin	1423	93.1	95.3	1.02		
<b>Albumin/creatinine ratio 30-300 mg/g (microalbuminuria)</b>						
Placebo	188	99.4	103.6	1.04	0.98	0.27
Canagliflozin	437	105.4	107.2	1.02		
<b>Albumin/creatinine ratio &gt;300 mg/g (macroalbuminuria)</b>						
Placebo	63	106.0	121.5	1.15	0.89	0.11
Canagliflozin	99	121.6	124.0	1.02		

IGFBP7, insulin-like growth factor binding protein-7.

\*Nominal *P* value on treatment effect on mean IGFBP7 fold-change from baseline.

**Supplemental Table 2.** Log-transformed IGFBP7 at Baseline and 1 Year Relative to Subsequent Outcomes in the CANVAS Study after adjusting for baseline medication.

Events	Per log-unit increase of IGFBP7							
	Baseline IGFBP7				1-year IGFBP7			
	HR <sub>adj</sub> (95% CI)*	<i>P</i>	C-index with Clinical covariates only	C-index with baseline IGFBP7 only	C-index with both (improvement from clinical covariates only)	HR <sub>adj</sub> (95% CI)*	<i>P</i>	C-index with Baseline and 1- year IGFBP7
Sustained decline in eGFR by 40% <sup>†</sup>	1.66 (0.79, 3.51)	0.18	0.72	0.69	0.73 (+0.01)	13.6 (6.5, <0.001 28.5)	0.78	0.80 (+0.05)
Progression to macroalbuminuria	2.09 (1.24, 3.53)	0.008	0.81	0.63	0.81 (0)	3.41 (1.60, 0.002 7.26)	0.67	0.81 (0)
First progression of albuminuria	1.66 (1.25, 2.21)	<0.001	0.58	0.56	0.59 (+0.01)	1.68 (1.11, 0.015 2.55)	0.58	0.59 (0)
Cardiovascular death	4.67 (2.71, 8.06)	<0.001	0.69	0.67	0.70 (+0.01)	2.20 (0.70, 0.18 6.85)	0.67	0.70 (0)
Renal composite <sup>‡</sup>	2.54 (1.15, 5.60)	0.021	0.72	0.70	0.74 (+0.02)	14.3 (6.90, <0.001 29.7)	0.78	0.81 (+0.04)

Renal composite plus cardiovascular death	3.58 (2.24, 5.70)	<0.001	0.69	0.67	0.71 (+0.02)	5.87 (3.38, 10.2)	<0.001	0.69	0.72 (+0.01)
Renal composite plus progression to macroalbuminuria	3.23 (2.08, 5.02)	<0.001	0.65	0.64	0.67 (+0.02)	6.94 (4.15, 11.6)	<0.001	0.69	0.70 (+0.02)

IGFBP7, insulin-like growth factor binding protein-7; eGFR, estimated glomerular filtration rate; HR<sub>adj</sub>, adjusted hazard ratio.

\*Covariates for adjustment were selected using the Bayesian information criterion in patients randomized to placebo in the main study along with baseline IGFBP7 and treatment allocation. Baseline medications adjusted for include baseline use of diuretic, sulphonylurea, GLP-1 receptor agonists, statins, insulin, metformin, RAAS inhibitors, and beta blocker. Improvement in the C-index was change above a base model of covariates excluding biomarker concentrations.

†40% decrease in eGFR was sustained for  $\geq 2$  consecutive measures.

‡The renal composite endpoint from CANVAS comprised a 40% decrease in eGFR (sustained for  $\geq 2$  consecutive measures), the need for renal replacement therapy (dialysis or transplantation), or renal death.

**Supplemental Table 3:** Dichotomous Baseline IGFBP7 and Subsequent Outcomes in the CANVAS Study. The median concentration of 96.5 ng/mL was used.

Event	Baseline IGFBP7 $\geq$ 96.5 ng/mL		
	HR <sub>adj</sub> (95% CI)	<i>P</i>	<i>P</i> <sub>interaction</sub>
Sustained reduction of eGFR by 40%*	2.49 (1.41, 4.39)	0.002	0.39
Progression to macroalbuminuria	1.79 (1.25, 2.58)	0.002	0.24
First progression of albuminuria	1.70 (1.39, 2.07)	<0.001	0.002
Cardiovascular death	2.09 (1.33, 3.30)	0.002	0.58
Renal composite <sup>†</sup>	2.80 (1.60, 4.89)	<0.001	0.25
Renal composite plus cardiovascular death	2.30 (1.61, 3.30)	<0.001	0.17
Renal composite plus progression to macroalbuminuria	2.15 (1.58, 2.94)	<0.001	0.42

IGFBP7, insulin-like growth factor binding protein-7; eGFR, estimated glomerular filtration rate.

\*40% decrease in eGFR was sustained for  $\geq$ 2 consecutive measures.

<sup>†</sup>The renal composite endpoint from CANVAS comprised a 40% decrease in eGFR (sustained for  $\geq$ 2 consecutive measures), the need for renal replacement therapy (dialysis or transplantation), or renal death.

**Supplemental Table 4.** Dichotomous 1-year IGFBP7 and Subsequent Outcomes in the CANVAS Study. Optimal Cut-off at Baseline for Predicting Risk was  $\geq 110.3$  ng/mL

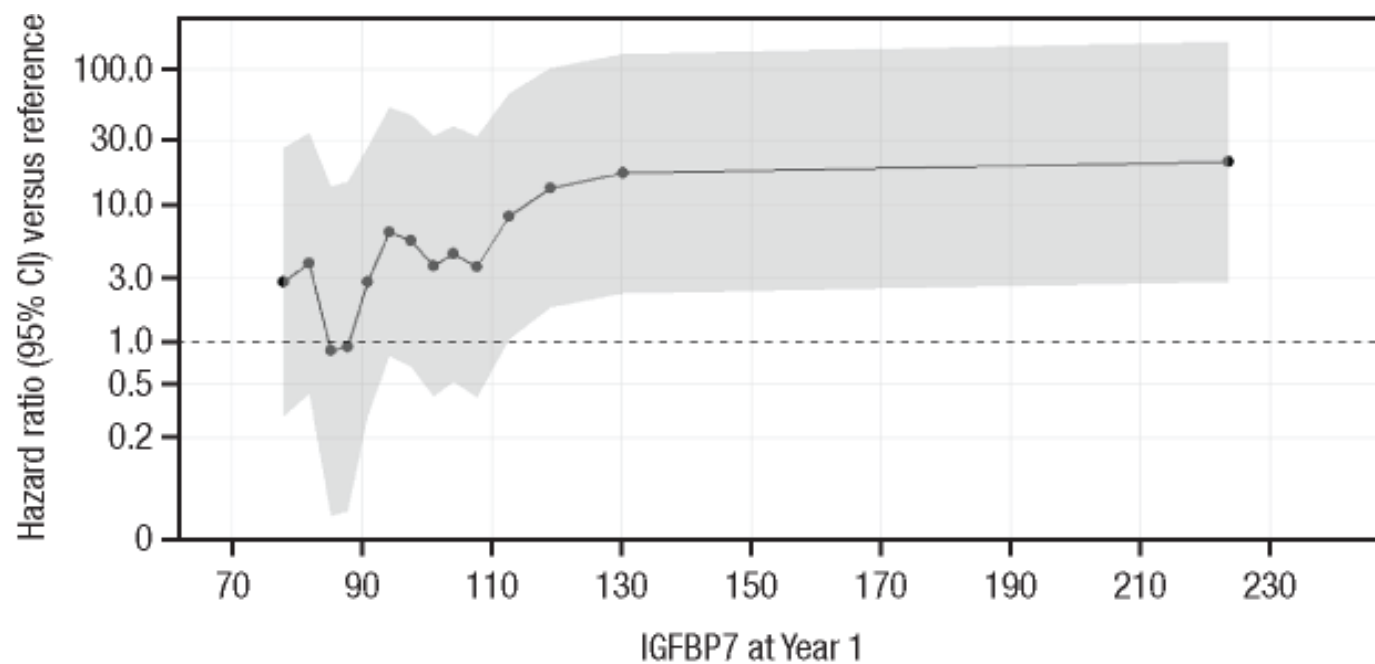
Event	1-year IGFBP7 $\geq 110.3$ ng/mL		
	HR <sub>adj</sub> (95% CI)	<i>P</i>	<i>P</i> <sub>interaction</sub>
Sustained reduction of eGFR by 40%*	2.86 (1.45, 5.62)	0.002	0.87
Progression to macroalbuminuria	2.19 (1.37, 3.52)	0.001	0.63
First progression of albuminuria	1.39 (1.08, 1.79)	0.01	0.29
Cardiovascular death	0.94 (0.51, 1.72)	0.84	0.91
Renal composite <sup>†</sup>	2.91 (1.48, 5.72)	0.002	0.60
Renal composite plus cardiovascular death	1.66 (1.04, 2.63)	0.03	0.60
Renal composite plus progression to macroalbuminuria	2.31 (1.54, 3.46)	<0.001	0.98

IGFBP7, insulin-like growth factor binding protein-7; eGFR, estimated glomerular filtration rate.

\*40% decrease in eGFR was sustained for  $\geq 2$  consecutive measures.

<sup>†</sup>The renal composite endpoint from CANVAS comprised a 40% decrease in eGFR (sustained for  $\geq 2$  consecutive measures), the need for renal replacement therapy (dialysis or transplantation), or renal death.

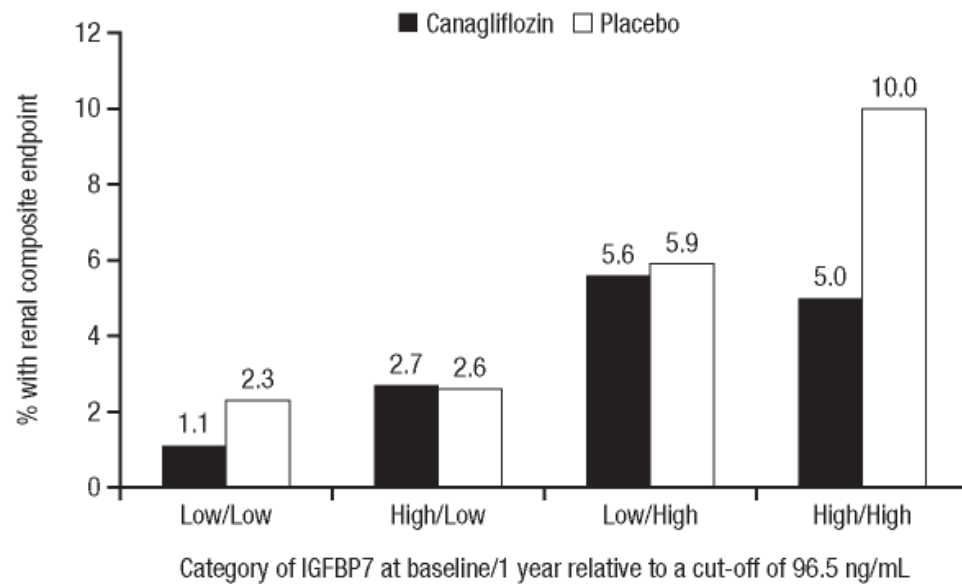
**Supplemental Figure 1.** HR for renal composite endpoint of the CANVAS study as a function of the IGFBP7 concentrations at 1 year in the study.



HR, hazard ratio; IGFBP7, insulin-like growth factor binding protein-7.



**Supplemental Figure 2.** Rates of the renal composite endpoint by end of study as a function of baseline IGFBP7 and treatment allocation. Those study participants with IGFBP7 concentrations above 96.5 ng/mL at baseline and 1 year had the highest risk for the renal composite endpoint. Among these patients, treatment allocation to canagliflozin was associated with the largest reduction of this outcome measure.



IGFBP7, insulin-like growth factor binding protein-7.