

Supplementary Table 2. Main characteristics of included trials

NCT number	Study	Trial phase	Acronym	No. of randomized patients	Study duration, wk	Target	Comparator(s)	Background medication	Population	Age, yr	Male gender	Baseline HbA1c, %	Mean duration of T2DM, yr
NCT01032629	Zhou et al. (2019) [1]	III	CANVAS of the CANVAS Pro-gram)	4,330	52	Canagliflozin 100 or 300 mg	PLB	Variable	Multinational	62.4±8.0	66.1%	8.2±0.9	13.4±7.5
NCT01989754	Zhou et al. (2019) [1]	IV	CANVAS-R of the CANVAS Program	5,813	78	Canagliflozin up to 300 mg	PLB	Variable	Multinational	64.0±8.4	62.8%	8.3±1.0	13.7±7.9
NCT01730534	Wiviott et al. (2019) [2]	III	DECLARE-TIMI 58	17,160	Median 4.2 yr	Dapagliflozin 10 mg qd	PLB	Variable	Multinational	DAPA: 63.9±6.8 PLB: 64.0±6.8	DAPA: 63.1% PLB: 3,251 (62.1)	DAPA: 8.3±1.2 PLB: 8.3±1.2	eGFR ≥90 10.9±7.2
NCT01897532	Rosenstock et al. (2019) [3]	IV	CARMELINA	6,991	Median 2.2 yr	Linagliptin 5 mg	PLB	Except DPP-4, GLP-1, and SGLT-2	Multinational	LINA: 66.1±9.1 PLB: 65.6±9.1	LINA: 2,148 (61.5) PLB: 2,242 (64.3)	LINA: 7.9±1.0 PLB: 8.0±1.0	LINA: 15.0±9.6 PLB: 14.5±9.3
NCT01243424	Rosenstock et al. (2019) [4]	III	CAROLINA	6,042	Median 6.3 yr	Linagliptin 5 mg qd	Glimepiride 1-4 mg qd	Näve, SU, or glinide as monotherapy or in a dual combination with MET or α -glucosidase inhibitor	Multinational	LINA: 63.9±9.5 GLIME: 64.2±9.5	LINA: 1,838 (60.8) GLIME: 1,781 (59.2)	LINA: 7.2±0.6 GLIME: 7.2±0.6	Median LINA: 6.3 GLIME: 6.2
NCT02065791	Mahaffey et al. (2019) [5]		CRENCE	4,401	Median 2.62 yr	Canagliflozin 100 mg qd	PLB	Variable	Multinational	CANA: 62.9±9.2 PLB: 63.2±9.2	CANA: 65.4% PLB: 66.7%	CANA: 8.3±1.3 PLB: 8.3±1.3	CANA: 15.5±8.7 PLB: 16.0±8.6
NCT02692716	Husain et al. (2019) [6]	III	PIONEER 6	3,183	Median 15.9 mo	Semaglutide up to 14 mg qd	PLB	Variable	Multinational	SEMA: 66±7 PLB: 66±7	SEMA: 68.1% PLB: 500 68.6%	SEMA: 8.2±1.6 PLB: 8.2±1.6	SEMA: 14.7±8.5 PLB: 15.1±8.5
NCT00894868	McMurray et al. (2018) [7]	IV	VIVID	254	52	Vildagliptin 50 mg bid (qd if concomitant use of SU)	PLB	Variable	Multinational	VILDA: 62.9±8.5 PLB: 63.4±10.2	VILDA: 77.3% PLB: 76.2%	VILDA: 9.5±8.1 PLB: 9.1±7.8	
NCT02465515	Hernandez et al. (2018) [8]		Harmony	9,463	Median 1.6 yr	Albiglutide 30-50 mg qw	PLB	Variable	Multinational	ALBI: 64.1±8.7 PLB: 64.2±8.7	ALBI: 3,304 (70) PLB: 3,265 (69)	ALBI: 8.76±1.5 PLB: 8.72±1.5	ALBI: 14.1±8.6 PLB: 14.2±8.9
NCT01144338	Holman et al. (2017) [9]	III	EXSCEL	14,752	Median 3.2 yr	Exenatide 2 mg qw	PLB	Variable	Multinational	EXEN: 62.0 PLB: 62.0	EXEN: 62.0% PLB: 62.0%	EXEN: 8.0 PLB: 8.0	EXEN: 12.0 PLB: 12.0
NCT01703208	Gantz et al. (2017) [10]	III	LEADER	4,202	Median 96	Omarigliptin 25 mg qw	PLB	Variable	Multi-center	OMARI: 63.7±8.5 PLB: 63.6±8.5	OMARI: 1,461 (69.6) PLB: 1,487 (70.7)	OMARI: 8.0±0.9 PLB: 8.0±0.9	OMARI: 12.0±7.6 PLB: 12.1±8.0
NCT01179048	Marso et al. (2016) [11]	III	LEADER	9,340	Median 3.8 yr	Liraglutide	PLB	Variable	Multinational	≥60 yr LIRA: 46.8±13.5 PLB: 52.8±14.9	LIRA: 425 (14.1) PLB: 485 (16.2)	>8.3 LIRA: 319±13.7 PLB: 361±16.1	>11 yr LIRA: 340±13.9 PLB: 376±15.3

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Supplementary Table 2. Continued

NCT number	Study	Trial phase	Acronym	No. of randomized patients	Study duration, wk	Target	Comparator(s)	Background medication	Population	Age, yr	Male gender	Baseline HbA1c, %	Mean duration of T2DM, yr
NCT01720446	Marso et al. (2016) [12]	III	SUSTAIN-6	3,297	109 (median 2.1 yr)	Semaglutide 0.5 or 1.0 mg qw	PLB	Variable	Multinational	SEMA 0.5 mg: 64.6±7.3 SEMA 1.0 mg: 64.7±7.1 PLB 0.5 mg: 64.8±7.6 PLB 1.0 mg: 64.4±7.5	SEMA: 1,013 PLB: 989	SEMA 0.5 mg: 8.7±1.4 SEMA 1.0 mg: 8.7±1.5 PLB: 8.7±1.5	SEMA 0.5 mg: 14.3±8.2 SEMA 1.0 mg: 14.1±8.2 PLB: 14.0±8.5 PLB 1.0 mg: 13.2±7.4
NCT01131676	Zinman et al. (2015) [13]	III	EMPA-REG OUT-COME	7,028	Median 3.1 yr	Empagliflozin 10 or 25 mg qd	PLB	Variable	Multinational	EMPA: 63.1±8.6 PLB: 63.2±8.8	EMPA: 3,336 (71.2) PLB: 1,680 (72.0)	EMPA: 8.07±0.85 PLB: 8.08±0.84	>10 yr EMPA: 2,672±57.0 PLB: 1,339±57.4
NCT01147250	Pfeffer et al. (2015) [14]	III	ELIXA	6,068	Median 25 mo	Lixisenatide upto 20 µg	PLB	Variable	Multinational	LIXI: 59.9±9.7 PLB: 60.6±9.6	LIXI: 69.6% PLB: 69.1%	LIXI: 7.7±1.3 PLB: 7.6±1.3	LIXI: 9.2±8.2 PLB: 9.4±8.3
NCT00790205	Green et al. (2015) [15]	III	TECOS	14,735	Median 3.0 yr	Sitagliptin 100 mg qd	PLB	Variable	Multinational	SITA: 65.4±7.9 PLB: 65.5±8.0	SITA: 70.9% PLB: 70.5%	SITA: 7.2±0.5 PLB: 7.2±0.5	Mean SITA: 11.6±8.1 PLB: 11.6±8.1
NCT01042977	Leiter et al. (2014) [16]	III		964	24	Dapagliflozin 10 mg qd	PLB	Variable	Multinational	DAPA: 63.9±7.6 PLB: 63.6±7.0	DAPA: 66.9% PLB: 67.0%	DAPA: 8.0±0.8 PLB: 8.1±0.8	DAPA: 13.5±8.2 PLB: 13.0±8.4
NCT01294423	Kaku et al. (2014) [17]	III		261	24	Dapagliflozin 5 or 10 mg	PLB	Variable	Multi-center	DAPA5: 58.6±10.4 DAPA10: 57.5±9.3 PLB: 60.4±9.7	DAPA5: 58.1 DAPA10: 53 (60.2) PLB: 52 (59.8)	DAPA5: 7.50±0.72 DAPA10: 7.46±0.61 PLB: 7.50±0.63	DAPA5: 4.59±5.56 DAPA10: 4.93±4.52 PLB: 5.29±6.17
NCT00968708	White et al. (2013) [18]	III	EXAMINE	5,380	Median 18 mo	Alogliptin 6.25, 12.5, or 25 mg	PLB	Variable	Multinational	Median ALO: 61.0 PLB: 61.0	ALO: 1,828 (67.7) PLB: 1,823 (68.0)	ALO: 8.0±1.1 PLB: 8.0±1.1	ALO: 7.1 PLB: 7.3
NCT01107886	Scirica et al. (2013) [19]	IV	SAVOR-TIMI 53	16,492	Median 2.1 yr	Saxagliptin 2.5 or 5.0 mg	PLB	Variable	Multinational	SAXA: 65.1±8.5 PLB: 65.0±8.6	SAXA: 66.6% PLB: 67.3%	SAXA: 8.0±1.4 PLB: 8.0±1.4	SAXA: 10.3 PLB: 10.3
NCT00513630	Hong et al. (2013) [20]	IV	SPREAD-DIMCAD	304	Median 5 yr	Glipizide (mean dose 28.3±3.9 mg)	Metformin (mean dose 1.4±0.2 mg)	Variable	Multi-center	GLIP: 63.8±9.4 MET: 62.8±8.5	GLIP: 114 (77.0) MET: 122 (78.2)	GLIP: 7.6±1.7 MET: 7.6±1.7	GLIP: 3.0±5.1 MET: 2.9±4.8
NCT00744926	Raz et al. (2012) [21]	III	T-emerge 1	373	24	Tasoglutide 10 or 20 mg qw	PLB	Variable	Multinational	TASPO10: 53.4±9.6 TASPO20: 55.0±10.4 PLB: 55.8±8.5	TASPO10: 41 (37) TASPO20: 46 (36) PLB: 43 (37)	TASPO10: 7.5±1.0 TASPO20: 7.7±1.0 PLB: 7.6±1.0	TASPO10: 2.8±2.9 TASPO20: 2.1±2.4 PLB: 2.3±1.9
NCT00116831	Gerstein et al. (2010) [22]	III	APPROACH	672	18 mo	Rosiglitazone upto 8 mg qd	Glipizide upto 15 mg qd	Variable	Multinational	ROSI: 61.8±8.4 GLIP: 60.2±9.0	ROSI: 233 (70.0) GLIP: 223 (65.8)	ROSI: 7.1±0.8 GLIP: 7.2±0.9	Median ROSI: 5.0 GLIP: 4.6

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NCT00484198	Chou et al. (2012) [23]	III		1,912	26	Rivoglitazone 1.0 or 1.5 mg or pioglitazone 45 mg qd	PLB		Multinational	RIVO1.0: 55.0±10.51 RIVO1.5: 55.1±10.59 PIO45: 55.0±10.84 PLB: 55.4±12.32	RIVO1.0: 132 (48.2) RIVO1.5: 382 (50.9) PIO45: 398 (53.0) PLB: 67 (48.9)	RIVO1.0: 7.7±0.53 RIVO1.5: 7.7±0.57 PIO45: 7.7±0.58 PLB: 7.7±0.54	RIVO1.0: 5.0±5.26 RIVO1.5: 4.3±4.40 PIO45: 4.4±4.99 PLB: 4.9±6.13
NCT00740051	Barnett et al. (2012) [24]	III		227	52	Linagliptin 5 mg qd	PLB/ Glimepiride 1-4 mg qd		Multinational	LINA: 56.4±10.6 PLBGLIME: 56.7±9.7	LINA: 55 (36.4) PLBGLIME: 33 (43.4)	LINA: 8.1±1.0 PLBGLIME: 8.1±0.9	>1-5 yr LINA: 75±51.0 PLBGLIME: 40±54.8
NCT00521742	Giles et al. (2010) [25]	III		300	52	Pioglitazone 15 mg	Glyburide 2.5 mg	With or without MET	Multi-center	64	56%	PIO: 8.6±1.5 GLYB: 8.3±1.4	
NCT00494312	Tolman et al. (2009) [26]	IV		2,120	3 yr	Pioglitazone upto 45 mg	Glibenclamide upto 15 mg	With or without MET	Multi-center	Median PIO: 54 GLIBE: 55	PIO: 601 (57.2) GLIBE: 581 (55.5)	PIO: 9.5±2.0 GLIBE: 9.5±2.0	PIO: 305±301 wk GLIBE: 292±280 wk
NCT00174993	Wilcox et al. (2007) [27]	III	PROactive	5,238	Mean 34.5 mo	Pioglitazone 15-45 mg	PLB	Variable	Multinational	No previous stroke: 61.6±7.7 Previous stroke: 62.3±7.5	No previous stroke: 2,867 (67) Previous stroke: 596 (61)	No previous stroke: 8.1±1.4 Previous stroke: 8.1±1.4	Median no previous stroke: 8.0 Previous stroke: 9.0
NCT00279045	Kahn et al. (2006) [28]	III	ADOPT	4,360	Median 4.0 yr	Rosiglitazone upto 4 mg bid	Metformin upto 1 g bid; Glyburide upto 7.5 mg bid		Multinational	ROSI: 56.3±10.0 MET: 57.9±9.9 GLYB: 56.4±10.2	ROSI: 811 (55.7) MET: 864 (59.4) GLYB: 836 (58.0)	ROSI: 7.36±0.93 MET: 7.36±0.93 GLYB: 7.35±0.92	<1 yr ROSI: 651±44.6 MET: 673±46.3 GLYB: 637±44.2
NCT00087516	Aschner et al. (2006) [29]	III		741	24 (+80) ^b	Sitagliptin 100 or 200 mg qd	PLB		Multinational	SITA100: 53.4±9.5 SITA200: 54.9±10.1 PLB: 54.3±10.1	SITA100: 136 (57.1) SITA200: 117 (46.8) PLB: 130 (51.4)	SITA100: 8.01±0.88 SITA200: 8.08±0.94 PLB: 8.03±0.82	4.4
NCT00707993		III		441	52	Glipizide 5 mg qd	Alogliptin 25 mg qd		Multi-center	GLIP: 69.8±4.07 ALO: 70.1±4.42	GLIP: 198 (44.9) ALO: 102 (45.9)	GLIP: 5.94±6.276 ALO: 6.25±6.285	
NCT01164501	Barnett et al. (2014) [30]	III		741	52	Empagliflozin 10 or 20 mg	PLB		Multinational	CKD III: 64.6±8.9 PLB: 65.1±8.2	CKD III: 107 (57.2) PLB: 106 (56.7)	CKD III: 8.02±0.84 PLB: 8.09±0.80	CKD III > 10 yr EMPA25: 129±69.0 PLB: 123±65.8
NCT00800683		III		133	52	Linagliptin 5 mg	PLB	Insulin with or without SU	Multinational	LINA: 64.0±10.9 PLB: 64.9±9.6	LINA: 45 (66.2) PLB: 35 (53.8)	LINA: 8.2±1.1 PLB: 8.2±0.9	

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NCT number	Study	Trial phase	Acronym	No. of randomized patients	Study duration, wk	Target	Comparator(s)	Background medication	Population	Age, yr	Male gender	Baseline HbA1c, %	Mean duration of T2DM, yr
NCT01106651	Bode et al. (2015) [31]	III		716	104	Canagliflozin 100 or 300 mg	PLB	Variable	Multi-center	CANA100: 64.3±6.46 CANA300: 63.4±5.99 PLB: 63.2±2.21	CANA100: 124 (51.5) CANA300: 129 (54.7) PLB: 143 (60.3)	CANA100: 7.8±0.8 CANA300: 7.7±0.8 PLB: 7.8±0.8	CANA100: 12.3±7.8 CANA300: 11.3±7.2 PLB: 11.4±7.3
NCT02025907		IV		218	26	Canagliflozin 100-300 mg	PLB	MET and sitagliptin	Multi-center	CANA: 57.4±9.28 PLB: 57.5±10.14	CANA: 66 (61.7) PLB: 55 (51.9)	8.5±0.8	9.9±5.7
NCT01064414		III		272	52	Canagliflozin 100 or 300 mg	PLB		Multi-center	CANA100: 69.5±8.2 CANA300: 67.9±8.24 PLB: 68.2±8.4	CANA100: 58 (64.4) CANA300: 48 (53.9) PLB: 57 (63.3)		
NCT01106625		III	CANTATA-MSU	469	52	Canagliflozin 100 or 300 mg	PLB	MET and SU	Multi-center	CANA100: 57.3±10.47 CANA300: 56±8.95 PLB: 56.7±8.36	CANA100: 76 (48.4) CANA300: 87 (55.8) PLB: 76 (48.7)		
NCT01081834	Stenlof et al. (2013) [32]	III	CANTATA-M	678	52	Canagliflozin 100 or 300 mg	PLB/Sitagliptin 100 mg		Multi-center	CANA100: 55.1±10.83 CANA300: 55.3±10.17 PLBSITA: 55.7±10.88	CANA100: 81 (41.5) CANA300: 89 (45.2) PLBSITA: 88 (45.8)	CANA100: 8.1±1.0 CANA300: 8.0±1.0 PLBSITA: 8.0±1.0	CANA100: 4.5±4.4 CANA300: 4.3±4.7 PLBSITA: 4.2±4.1
NCT00094757		III		521	54	Sitagliptin 100 or 200 mg	PLB/Pioglitazone 30 mg qd		Multi-center	SITA100: 54.5±10.0 SITA300: 55.4±9.2 PLBPIO: 55.5±10.1	SITA100: 110 (53.7) SITA300: 104 (50.5) PLBPIO: 69 (62.7)	SITA100: 8.0±0.8 SITA300: 8.1±0.9 PLBPIO: 8.0±0.9	DAPA: 14.3±8.1 PLB: 14.5±8.3
NCT02413398	Fioretto et al. (2018) [33]	III	DERIVE	321	24	Dapagliflozin 10 mg	PLB	Variable	Multinational	DAPA: 65.3 PLB: 66.2	DAPA: 91 (56.9) PLB: 91 (56.5)	DAPA: 8.33±1.08 PLB: 8.03±1.08	DAPA5: 1.15±2.3 DAPA10: 1.67±2.8 PLB: 1.30±2.0
NCT01095653	Ji et al. (2014) [34]	III		393	24	Dapagliflozin 5 or 10 mg	PLB		Multinational	DAPAS: 53.0±11.07 DAPA10: 51.2±9.89 PLB: 49.9±10.87	DAPAS: 84 (65.6) DAPA10: 86 (64.7) PLB: 87 (65.9)	DAPAS: 8.14±0.74 DAPA10: 8.28±0.95 PLB: 8.35±0.95	DAPAS: 1.15±2.3 DAPA10: 1.67±2.8 PLB: 1.30±2.0
NCT00663260	Kohan et al. (2014) [35]	II/III		252	104	Dapagliflozin 5 or 10 mg	PLB	Variable	Multinational	DAPAS: 66±8.9 DAPA10: 68±7.7 PLB: 67±8.6	DAPAS: 55 (66.3) DAPA10: 56 (65.9) PLB: 53 (63.1)	DAPAS: 8.30±1.04 DAPA10: 8.22±0.98 PLB: 8.53±1.28	DAPAS: 16.9±9.0 DAPA10: 18.2±10.1 PLB: 15.7±9.5

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Supplementary Table 2. Continued

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NCT01031680	Cefalu et al. (2015) [36]	III		922	52	Dapagliflozin 10 mg	PLB	Variable excluding rosiglitazone	Multinational	DAPA: 62.8±7.0 PLB: 63.0±7.7	DAPA: 67.9% PLB: 68.6%	DAPA: 8.18±0.84 PLB: 8.08±0.80	DAPA: 12.6±8.7 PLB: 12.3±8.2
NCT02182830	Ferdinand et al. (2019) [37]	III		166	24	Empagliflozin 10–25 mg qd	PLB	Variable	Multi-center	EMPA: 56.5±9.3 PLB: 57.2±9.3	EMPA: 43 (55.1) PLB: 36 (50.0)	EMPA: 8.66±0.11 PLB: 8.51±0.13	EMPA: 9.3±6.2 PLB: 9.3±7.9
NCT01986855	Grunberger et al. (2018) [38]	III	VERTISRE-NAL	468	52	Ertugliflozin 5 or 15 mg qd	PLB	Variable (except MET, rosiglitazone, and other SGLT-2)	Multinational	ERTU5: 66.7±8.3 ERTU15: 67.5±8.5 PLB: 67.5±8.9	ERTU5: 84 (53.2) ERTU15: 75 (48.4) PLB: 72 (46.8)	ERTU5: 8.2±1.0 ERTU15: 8.2±0.9 PLB: 8.1±0.9	ERTU5: 14.9±9.0 ERTU15: 14.5±8.5 PLB: 13.1±8.1
NCT00676338	Russell-Jones et al. (2012) [39]	III	DURATION-4	820	26	Exenatide 2 mg qw	Metformin 2,000 mg qd; Pioglitazone 45 mg qd; Sitagliptin 100 mg qd		Multinational	EXEN: 54±11 MET: 54±11 PIO: 55±11 SITA: 52±11	EXEN: 139 (56.0) MET: 154 (62.6) PIO: 97 (59.5) SITA: 94 (57.7)	EXEN: 8.5±1.2 MET: 8.6±1.2 PIO: 8.5±1.2 SITA: 8.5±1.3	EXEN: 2.7±3.2 MET: 2.6±3.6 PIO: 2.7±3.7 SITA: 2.7±3.7
NCT01087502	Laakso et al. (2015) [40]	III		235	52	Linagliptin 5 mg qd	PLB/ Glimepiride 1–4 mg qd	Variable	Multinational	LINA: 67.3±9.2 PLBGLIME: 65.9±9.4	LINA: 70 (61.9) PLBGLIME: (64.8)	LINA: 8.08±0.89 PLBGLIME: 8.03±0.94	LINA: 8.08±0.89 PLBGLIME: 8.03±0.94
NCT00601250		III		701	24	Linagliptin 5 mg qd	PLB		Multinational	LINA: 56.5±10.1 PLB: 56.6±10.9	LINA: 278 (53.2) PLB: 101 (57.1)	LINA: 8.09±0.86 PLB: 8.02±0.88	
NCT01084005	Barnett et al. (2013) [41]	III		241	24	Linagliptin 5 mg qd	PLB	Variable	Multinational	LINA: 74.9±4.4 PLB: 74.9±4.2	LINA: 116 (71.6) PLB: 49 (62.0)	LINA: 7.8±0.8 PLB: 7.7±0.7	LINA: > 10 yr LINA: 89±55.6 PLB: 42±53.8
NCT01620489	Davies et al. (2016) [42]	III	LIRA-RE-NAL	279	26	Liraglutide 1.8 mg qd	PLB	Variable	Multinational	LIRA: 68.0±8.3 PLB: 66.3±8.0	LIRA: 75 (53.6) PLB: 65 (47.4)	LIRA: 8.08±0.792 PLB: 8.00±0.853	LIRA: 15.9±8.9 PLB: 14.2±7.5
NCT01798706	Menelly et al. (2017) [43]	III	GetGoal-O	350	24	Lixisenatide 20 µg	PLB	Variable	Multinational	LIXI: 74.0±4.0 PLB: 74.4±3.8	LIXI: 92 (52.3) PLB: 90 (51.7)	LIXI: 8.1±0.7 PLB: 8.1±0.7	LIXI: 13.6±7.3 PLB: 14.6±7.9
NCT01126580	Umpierrez et al. (2014) [44]	III	AWARD-3	807	52	Dulaglutide 0.75 or 1.5 mg qw	Metformin upto 2,000 mg qd		Multinational	DULA0.75: 56±11 DULA1.5: 56±10	DULA0.75: (44) DULA1.5: (42)	DULA0.75: 7.6±0.9 DULA1.5: 7.6±0.9	DULA0.75: 3±2 DULA1.5: 3±2 MET: 3±2
NCT01704261	Lee et al. (2017) [45]	III		307	24	Omarigliptin 25 mg qw	PLB	MET ≥ 1,500 mg qd and glimepiride or another SU	Multinational	OMARI: 57.2±8.4 PLB: 58.4±9.4	OMARI: (47.4) PLB: (48.4)	OMARI: 8.5±0.8 PLB: 8.6±0.8	OMARI: 9.8±5.3 PLB: 10.4±5.5

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Supplementary Table 2. Continued

NCT number	Study	Trial phase	Acronym	No. of randomized patients	Study duration, wk	Target	Comparator(s)	Background medication	Population	Age, yr	Male gender	Baseline HbA1c, %	Mean duration of T2DM, yr
NCT01698775	Chacra et al. (2017) [46]	III		213	24	Omarigliptin 12.5 or 25 mg	PLB/Glipizide 20 mg qd		Multinational	OMARI: 65.9±9.4 PLBGLIP: 64.5±9.7	OMARI: 68 (63.6) PLBGLIP: 63 (59.4)	OMARI: 8.3±0.8 PLBGLIP: 8.3±0.8	OMARI: 14.9±8.2 PLBGLIP: 15.1±8.7
NCT00225277	Nissen et al. (2008) [47]	III	PERISCOPE	547	72	Glimepiride 1–4 mg	Proglitazone 15–45 mg		Multinational	GLIME: 59.7±9.1 PIO: 60.0±9.4	GLIME: 180 (65.9) PIO: 186 (68.9)	GLIME: 7.4±1.0 PIO: 7.4±1.0	Median GLIME: 71.0±30.0–131.0 m PIO: 70.0±27.0–129.0 m
NCT01177813	Roden et al. (2013) [48]	III		899	24	Empagliflozin 10 or 25 mg qd	PLB/Sitagliptin 100 mg qd		Multinational	EMPA10: 56.2±11.6 EMPA25: 53.8±11.6	EMPA10: 142 (63) EMPA25: 145 (65)	EMPA10: 7.87±0.88 EMPA25: 7.86±0.85	>1–5 yr EMPA10: 92±41 EMPA25: 83±37 SITA: 86±39 PLB: 104±46
NCT01210001	Kovacs et al. (2015) [49]	III	EMPA-REG EXTEND PIO	499	76	Empagliflozin 10 or 25 mg	PLB	Proglitazone with or without MET	Multinational	EMPA10: 54.7±9.9 EMPA25: 54.2±8.9 PLB: 54.6±10.5	EMPA10: 83 (50.3) EMPA25: 85 (50.6) PLB: 73 (44.2)	EMPA10: 8.07±0.89 EMPA25: 8.06±0.82 PLB: 8.16±0.92	>1–5 yr EMPA10: 60±36.4 EMPA25: 76±45.2 PLB: 78±47.3
NCT02240680	Araki et al. (2019) [50]	IV		102	52	Linagliptin 5 mg qd	PLB	Variable	Multinational	LINA: 71.1±5.5 PLB: 71.5±5.6	LINA: 34 (65.4) PLB: 36 (72.0)	LINA: 8.1±0.8 PLB: 8.0±0.7	>15 yr LINA: 24±47.1 PLB: 22±44.0
NCT01792518	Groop et al. (2017) [51]	III	MARLINA-T2D	360	24	Linagliptin 5 mg qd	PLB	Variable	Multinational	LINA: 61.0±10.0 PLB: 60.1±9.3	LINA: 116 (63.7) PLB: 113 (63.5)	LINA: 7.82±0.87 PLB: 7.86±0.89	>10 yr LINA: 97±53.9 PLB: 71±40.8
NCT00679939	Bilezikian et al. (2013) [52]	IV		226	52	Rosiglitazone 8 mg minimum	Metformin 2,000 mg minimum		Multi-center	ROSI: 63.6±6.61 MET: 64.0±6.46	0.00%	ROSI: 6.8±0.73 MET: 6.8±0.74	ROSI: 3.9 MET: 3.3
NCT00698932		III		568	24	Saxagliptin 5 mg qd	PLB		Multinational	SAXA: 51.23±10.04 PLB: 51.57±10.34	SAXA: 160 (56.3) PLB: 155 (54.6)	SAXA: 9.15±0.125 PLB: 9.05±0.141	
NCT00614939	Nowicki et al. (2011) [53]	III		170	52	Saxagliptin 2.5 mg qd	PLB	Variable	Multi-center	SAXA: 66.8±8.3 PLB: 66.2±9.1	SAXA: 32 (37.6) PLB: 41 (48.2)	SAXA: 8.5±1.2 PLB: 8.1±1.1	SAXA: 15.1±7.5 PLB: 18.2±8.5
NCT00121641	Rosenstock et al. (2009) [54]	III		403	24 (+42 mo) ^a	Saxagliptin 2.5, 5, or 10 mg	PLB		Multi-center	SAXA2.5: 53.27±10.06 SAXA5: 53.91±11.57 SAXA10: 52.72±11.27	SAXA2.5: 58 (56.9) SAXA5: 54 (50.9) SAXA10: 45 (45.9) PLB: 47 (49.5)	SAXA2.5: 7.9±0.9 SAXA5: 8.0±1.1 SAXA10: 7.8±0.9 PLB: 7.9±0.9	SAXA2.5: 3.1±3.5 SAXA5: 2.5±3.3 SAXA10: 2.3±3.1 PLB: 2.3±2.7

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Supplementary Table 2. Continued

NCT number	Study	Trial phase	Acronym	No. of randomized patients	Study duration, wk	Target	Comparator(s)	Background medication	Population	Age, yr	Male gender	Baseline HbA1c, %	Mean duration of T2DM, yr
NCT00316082	Frederich et al. (2012) [55]	III		366	76	Saxagliptin 2.5 mg AM, 5 mg AM, 2.5-5 mg AM, or 5 mg PM	PLB		Multinational	SAXA2.5: 55.2±10.44 SAXA5: 54.7±9.71 SAXA2.5-5: 54.3±10.93 SAXA5P: 55.1±10.35 PLB: 55.6±10.32	SAXA2.5: 25 (33.8) SAXA5: 38 (51.4) SAXA2.5-5: 37 (52.1) SAXA5P: 33 (45.8) PLB: 35 (47.3)	SAXA2.5: 8.0±0.8 SAXA5: 8.0±0.9 SAXA2.5-5: 8.0±1.1 SAXA5P: 7.9±0.9 PLB: 7.8±1.0	SAXA2.5: 1.2±1.6 SAXA5: 1.7±2.4 SAXA2.5-5: 2.0±2.9 SAXA5P: 2.0±5.2 PLB: 1.7±2.8
NCT02054897	Sorli et al. (2017) [56]	III	SUSTAIN-1	388	30	Semaglutide 0.5 or 1.0 mg	PLB		Multinational	54.6±11.1 52.7±11.9 PLB: 53.9±11.0	SEMA0.5: 60 (47) SEMA1.0: 80 (62) PLB: 70 (54)	SEMA0.5: 8.09±0.89 SEMA1.0: 8.12±0.81 PLB: 7.95±0.85	SEMA0.5: 4.81±6.10 SEMA1.0: 3.62±4.88 PLB: 4.06±5.48
NCT01930188	Ahren et al. (2017) [57]	III	SUSTAIN-2	1,231	56	Semaglutide 0.5 or 1.0 mg	Sitagliptin 100 mg MET, TZD, or both		Multinational	54.8±10.2 56.0±9.4 SITA: 54.6±10.4	SEMA0.5: 207 (51) SEMA1.0: 205 (50) SITA: 208 (51)	SEMA0.5: 8.0±0.9 SEMA1.0: 8.0±0.9 SITA: 8.2±0.9	SEMA0.5: 6.4±4.7 SEMA1.0: 6.7±5.6 SITA: 6.6±5.1
NCT02532855	Scott et al. (2018) [58]	III	CompoSIT-R	614	24	Sitagliptin 100 mg qd	Dapa-gliflozin upto 10 mg	MET with or without SU	Multinational	67.7±8.5 66.6±8.6	SITA: 55.0 DAPA: 60.8	SITA: 7.7±0.7 DAPA: 7.8±0.7	SITA: 10.5±7.0 DAPA: 10.7±7.4
NCT00509262	Arjona Ferreira et al. (2013) [59]	III		426	54	Sitagliptin 25 or 50 mg qd upto 20 mg qd	Glipizide		Multinational	64.8±10.6 64.3±9.2	SITA: 80 (59.3) GLIP: 78 (54.9)	SITA: 7.8±0.7 GLIP: 7.8±0.7	SITA: 10.7±7.5 GLIP: 10.1±7.8
NCT00225264	Mazzone et al. (2006) [60]	III	CHICAGO	462	72	Pioglitazone 15-45 mg qd	Glinepiride 1-4 mg qd	Variable	Multi-center	59.3±8.0 59.9±8.2	PIO: 146 (63.5) GLIME: 143 (62.7)	PIO: 7.43±0.99 GLIME: 7.40±0.97	PIO: 8.0±7.6 GLIME: 7.5±6.8
NCT02827708	Mosenzon et al. (2019) [61]	III	PIONEER 5	324	26	Semaglutide 14 mg	PLB	Variable	Multinational	71±8 70±8	SEMA: 83 (51) PLB: 73 (45)	SEMA: 8.0±0.7 PLB: 7.9±0.7	SEMA: 14.1±8.6 PLB: 13.9±7.4
NCT02906930	Aroda et al. (2019) [62]	III	PIONEER 1	703	26	Oral semaglutide 3, 7, or 14 mg	PLB		Multinational	55±11 56±11 54±11	SEMA3: 89 (50.9) SEMA7: 93 (53.1) SEMA14: 86 (49.1) PLB: 89 (50.0)	SEMA3: 7.9±0.7 SEMA7: 8.0±0.6 SEMA14: 8.0±0.7 PLB: 7.9±0.7	SEMA3: 3.8±5.3 SEMA7: 3.6±5.1 SEMA14: 3.4±4.4 PLB: 3.4±4.6
NCT00138619	Rosenstock et al. (2009) [63]	III		598	80	Vildagliptin 50 mg bid	Rosiglitazone 8 mg qd		Multinational	54.41±11.56 ROSI: 54.18±10.87	VILDA: 228 (57.6) ROSI: 110 (54.5)	VILDA: 8.58±1.10 ROSI: 8.63±1.17	VILDA: 1.98±2.88 ROSI: 2.60±4.19

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Supplementary Table 2. Continued

NCT number	Study	Trial phase	Acronym	No. of randomized patients	Study duration, wk	Target	Comparator(s)	Background medication	Population	Age, yr	Male gender	Baseline HbA1c, %	Mean duration of T2DM, yr
NCT00138567	Goke et al. (2008) [64]	III		780	52	Vildagliptin 100 mg qd	Metformin 2,000 mg qd		Multinational	VILDA: 52.8±11.7 MET: 53.6±10.2	VILDA: 278 (52.9) MET: 146 (57.5)	VILDA: 8.7±1.1 MET: 8.7±1.1	Median VILDA: 1.05 MET: 1.03
NCT01986881	Cannon et al. (2020) [65]		VERTIS CV	8,250	3.5 yr	Ertugliflozin 5 or 15 mg	PLB	Variable	Multi-center	ERTU: 64.4±8.1 PLB: 64.4±8.0	ERTU: 3,866 (70.3) PLB: 1,903 (69.3)	ERTU: 8.2±1.0 PLB: 8.2±0.9	ERTU: 12.9±8.3 PLB: 13.1±8.4
NCT01394952	Gerstein et al. (2020) [66]		REWIND	9,901	Median 5.4 yr	Dulaglutide 1.5 mg qw	PLB	Variable	Multinational	DULA: 66.2±6.5 PLB: 66.2±6.5	DULA: 2,643 (53.4) PLB: 2,669 (53.9)	DULA: 7.3±1.1 PLB: 7.4±1.1	DULA: 10.5±7.3 PLB: 10.6±7.2
NCT03315143	Bhatt et al. (2021) [67]		SCORED	10,584	Median 16 mo	Sotagliflozin 200 mg	PLB	Variable	Multinational	SOTA: 69 PLB: 69	SOTA: 55.7% PLB: 54.5%	Median SOTA: 8.3 PLB: 8.3	
NCT02924064	Ji et al. (2021) [68]			247	24	Teneligliptin 20 mg	PLB	MET	Multi-center	TENE: 56.0±9.8 PLB: 54.7±10.1	TENE: 81 (66.4) PLB: 67 (54.0)	TENE: 7.9±0.68 PLB: 7.87±0.72	TENE: 5.05±3.90 PLB: 5.41±4.22
NCT03521934	Bhatt et al. (2021) [69]		SOLOIST-WHF	1,222	Median 9 mo	Sotagliflozin 200 mg	PLB	Variable	Multinational	Median SOTA: 69 PLB: 70	SOTA: 67.4% PLB: 65.1%	Median SOTA: 7.1 PLB: 7.2	

Values are presented as mean ± standard deviation or number (%).

HbA1c, glycosylated hemoglobin; T2DM, type 2 diabetes mellitus; CANVAS, CANagliflozin cardiovascular Assessment Study; PLB, placebo; CANVAS-R, CANagliflozin cardiovascular Assessment Study- Renal; DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58; qd, once a day; DAPA, dapagliflozin; eGFR, estimated glomerular filtration rate; CARMELINA, Cardiovascular safety and Renal Microvascular outcome study with LINagliptin; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT-2, sodium-glucose cotransporter-2; LINA, linagliptin; CAROLINA, Cardiovascular Outcome Study of Linagliptin vs Glimepiride in Type 2 Diabetes; MET, metformin; GLIME, glimepiride; CREDEnce, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; CANA, canagliflozin; ALBI, albiglutide; gw, once a week; EXSCeL, Exenatide Study of Cardiovascular Event Lowering Trial; EXEN, exenatide; OMARI, omarigliptin; function Diabetes; bid, two times a day; VILDA, vildagliptin; ALBI, albiglutide; gw, once a week; EXSCeL, Exenatide Study of Cardiovascular Event Lowering Trial; EXEN, exenatide; OMARI, omarigliptin; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; LIRA, liraglutide; SUSTAIN, Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 diabetes Mellitus Patients; EMPA, empagliflozin; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; LIXI, lixisenatide; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin; SITA, sitagliptin; DAPA, dapagliflozin; EXAMINE, Cardiovascular Outcomes Study of Alogliptin in Patients With Type 2 Diabetes and Acute Coronary Syndrome; ALO, alogliptin; SAVOR-TIMI 53, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53; SAXA, saxagliptin; SPREAD-DIMCAD, Study on the Prognosis and Effect of Anti-diabetic Drugs on Type-2 Diabetes Mellitus With Coronary Artery Disease; GLIP, glipizide; TASPO, tasoglutide; APPROACH, Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in diabetes patients with Cardiovascular History; ROSI, rosiglitazone; RIVO, rivoglitazone; PIO, pioglitazone; LINA, linagliptin; PLBGLIME, placebo and glimepiride; GLIBE, glibenclamide; PROactive, PROspective pioglitazone Clinical Trial In macroVascular Events; ADOPT, A diabetes outcome progression trial; GLXB, glyburide; CKD, chronic kidney disease; EMPA, empagliflozin; CANA, canagliflozin; CANTATA-MSU, CANagliflozin Treatment And Trial Analysis - Metformin and Sulphonylurea; CANTATA-M, CANagliflozin Treatment and Trial Analysis - Monotherapy; PLBSITA, placebo and sitagliptin; PLBPIO, placebo and pioglitazone; DERIVE, Dapagliflozin on Blood Glucose Level and Renal Safety in Patients With Type 2 Diabetes; VERTIS RENAL, eValuation of Ertugliflozin efficacy and Safety in Patients with Stage 3 Chronic Kidney Disease and Type 2 Diabetes Mellitus; ERTU, ertugliflozin; LIRA-RENAL, Liraglutide Versus Placebo as Add-on to Glucose-Lowering Therapy in Patients With Type 2 Diabetes and Moderate Renal Impairment; GetGoal-O, Lixisenatide Therapy in Older Patients With Type 2 Diabetes Inadequately Controlled on Their Current Antidiabetic Treatment; AWARD-3, Dulaglutide Monotherapy Versus Metformin in Type 2 Diabetes; DULA, dulaglutide; PERISCOPE, Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation; EMPA-REG EXTEND PIO, Extension of Empagliflozin as Add-on Therapy to Pioglitazone With or Without Metformin in Patients With Type 2 Diabetes Mellitus; MARLINA-T2D, Efficacy, Safety & Modification of Albuminuria in Type 2 Diabetes Subjects with Renal Disease with LINAglipitin; ComposIT-R, comparison of sitagliptin with dapagliflozin in mild renal impairment; CHICAGO, Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone; VERTIS CV, eValuation of Ertugliflozin efficacy and Safety CardioVascular outcomes trial; REWIND, Dulaglutide and cardiovascular outcomes in type 2 diabetes; SCORED, Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk; SOTA, sotagliflozin; TENE, teneligliptin; SOLOIST-WHF, Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure.