

S2 Table. Characteristics of included randomized double-blind placebo-controlled studies

Study, design, participants	Study duration ^a (week)	Study arms	n	Mean age (years)	Women proportion, n (%)	Baseline BMI (kg/m ²)	Baseline HbA1c (%)	Mean DM duration (years)	Primary and secondary outcomes
Davies, 2021[1]. STEP 2 Phase 3 trial. Obesity/overweight type 2 DM	68	Semaglutide 1.0 mg sc qw	404	55	203 (50.4)	35.3 (5.9)	8.1 (0.8)	7.7 (5.9)	(1) BW change, achieve goal rate (2) HbA1C, FPG, serum insulin, BMI, WC change, achieve goal rate ^d , BP, HR, lipids profiles, hsCRP, PAI-1, calcitonin, amylase, lipase, QoL, AE
		Semaglutide 2.4 mg sc qw	403	56	223 (55.2)	35.9 (6.4)	8.1 (0.8)	8.2 (6.2)	
		Placebo	403	55	190 (47.1)	35.9 (6.5)	8.1 (0.8)	8.2 (6.2)	
Gudbergson, 2021[2]. LOSEIT Phase 4 trial. Osteoarthritis /Obesity	52	Liraglutide 3 mg/day sc	80	59.2 (10.8)	52 (65)	32.8 (5.5)	NR	NA	(1) BW change, KOOS pain subscale (2) BMI, WC, waist/hip circumference ratio change, KOOS, ICOAP, WOMAC
		Placebo	76	59.3 (9.7)	49 (64)	31.3 (4.0)	NR	NA	
Neeland, 2021[3]. Phase 4 trial. Obesity/overweight	40	Liraglutide 3.0 mg/day sc qd	73	49.6 (9.8)	67 (92%)	37.2 (6.0)	NR	NA	(1) VAT reducing percentage (2) VAT volume, BW, WC, body adipose tissue, liver fat, lean body volume, muscle volume, FBG, insulin change
		Placebo	55	50.9 (8.8)	51 (93%)	38.1 (6.1)	NR	NA	
Wadden, 2021[4].	68	Semaglutide 2.4 mg sc qw	407	46	315 (77.4)	38.1 (6.7)	5.7 (0.3)	NA	(1) BW change, achieve goal rate

(STEP 3 Phase 3 trial). Obesity/over weight		Placebo	204	46	180 (88.2)	37.8 (6.9)	5.8 (0.3)		(2) HbA1C, FPG, fasting serum insulin, BW, BMI, WC change, achieve goal rate, BP, HR, lipids profiles, hsCRP, PAI-1, calcitonin, amylase, lipase, QoL, AE
Wilding, 2021[5]. STEP 1 Phase 3 trial. Obesity/over weight	68	Semaglutide 2.4 mg sc qw	1,306	46 (13)	955 (73.1)	37.8 (6.7)	5.7 (0.3)	NA	(1) BW change, achieve goal rate (2) HbA1C, FPG change, achieve goal rate, fasting insulin, WC change, achieve goal rate, fat mass, lean body mass, BP, HR, lipid profiles, hsCRP, PAI-1, calcitonin, soluble leptin receptor, leptin, aminotransferase ratio, QoL, AE
		Placebo	655	47 (12)	498 (76.0)	38.0 (6.5)	5.7 (0.3)		
Garvey, 2020[6]. SCALE™ Insulin Phase 3 trial. Obesity/over weight type 2 DM with basal insulin	56	Liraglutide 3.0 mg/day sc qd	198	55.9	108 (54.5)	35.9 (6.5)	7.9 (1.1)	11.4 (6.8)	(1) BW change, achieve goal rate (2) HbA1C, FPG, SMBG change, achieve goal rate, total daily insulin dose, WC change, achieve goal rate, BP, HR, lipid profiles, EKG, hematology, biochemistry changes, QoL, AE
		Placebo	198	57.6	99 (50.0)	35.3 (5.8)	8.0 (1.0)	12.8 (6.9)	
Ghanim, 2020[7]. Phase 3 trial. Overweight, type 1 DM	26	Liraglutide 1.8 mg/day sc qd	37	47 (2)	20 (65)	33.3 (1.2)	8.0 (0.2)	NR	(1) HbA1C (2) glucose at week 26
		Placebo	27	45 (3)	16 (59)	29.5 (1.3)	7.8 (0.2)		

Aroda, 2019[8]. PIONEER 1 Phase 3 trial. Type 2 DM treated with diet and exercise only	26	Semaglutide 3 mg oral qd	175	55 (11)	86 (49.1)	31.8 (6.3)	7.9 (0.7)	3.8 (5.3)	(1) HbA1C change (2) BMI, WC, FPG, SMBG change, achieve goal rate, insulin, pro-insulin, glucagon, HOMA, time to rescue medication, anti-Semaglutide antibodies (3) BP, HR, lipid profiles, Amylase, Lipase, CRP, changes, AE, QoL
		Semaglutide 7 mg oral qd	175	56 (11)	82 (46.9)	31.6 (6.4)	8.0 (0.6)	3.6 (5.1)	
		Semaglutide 14 mg oral qd	175	54 (11)	89 (50.9)	31.7 (6.6)	8.0 (0.7)	3.4 (4.4)	
		Placebo	178	54 (11)	89 (50.0)	32.2 (6.9)	7.9 (0.7)	3.4 (4.6)	
Gerstein, 2019[9]. REWIND Phase 3 trial. Type 2 DM, CVD	Median 64.8	Dulaglutide 1.5mg sc qw	4,949	66.2 (6.5)	2,306 (46.6)	32.3 (5.7)	7.3 (1.1)	10.5 (7.3)	(1) MACE, MI, stroke, CV-death (2) Angina, HF, microvascular
		Placebo	4,952	66.2 (6.5)	2,283 (46.1)	32.3 (5.8)	7.4 (1.1)	10.6 (7.2)	
Husain, 2019[10] PIONEER-6 Phase 3 trial. Type 2 DM, high CVD risk	Median 15.9 months	Semaglutide 14 mg oral qd	1,591	66 (7)	507 (31.9)	32.3 (6.6)	8.2 (1.6)	14.7 (8.5)	(1) MACE (2) MI, stroke, death, angina, HF, microvascular, HbA1C, BW change, BP, HR, lipid profiles, AE
		Placebo	1,592	66 (7)	500 (31.4)	32.3 (6.4)	8.2 (1.6)	15.1 (8.5)	
Mosenzonl, 2019[11]. PIONEER 5 Phase 3 trial.	26	Semaglutide 14 mg oral qd	163	71 (8)	80 (49)	32.2 (5.4)	8.0 (0.7)	14.1 (8.6)	(1) HbA1C change (2) FPG change, achieve goal rate, time to rescue medication, anti-semaglutide antibodies, BW, BMI, WC change, achieve goal rate, BP, HR, UACR, ECG, CRP, lipid
		Placebo	161	70 (8)	88 (55)	32.6 (5.5)	7.9 (0.7)	13.9 (7.4)	

Type 2 DM, CKD									profiles, amylase, lipase, AE, QoL
van Eyk, 2019[12] MAGNA VICTORIA Phase 4 trial. Type 2 DM	26	Liraglutide 1.8 mg/day sc qd	22	55 (11)	14 (64)	30.4 (3.8)	8.1 (0.9)	19 (10)	(1) Stroke volume, ejection fraction, cardiac output and index, peak ejection rate
		Placebo	25	55 (9)	14 (56)	28.6 (4.0)	8.6 (1.1)	17 (10)	(2) Aorta, carotid vessel wall imaging, adipose tissue distribution, total body fat, epicardial fat volume, HbA1c, FBG, BW, BMI change
Zinman, 2019[13] SUSTAIN 9 Phase 3 trial. Type 2 DM	30	Semaglutide 1.0 mg sc qw	151	57.5 (8.9)	62 (41.1)	31.1 (6.2)	8.0 (0.8)	9.8 (6.3)	(1) HbA1C change
		Placebo	151	56.6 (10.1)	64 (42.4)	32.7 (6.9)	8.1 (0.8)	9.6 (5.9)	(2) BW, FPG, SMPG, lipid, BMI, WC, hematology, biochemistry, calcitonin, EKG, HR, PE changes, PRO, AE
Zinman, 2019[14] PIONEER 8 Phase 3 trial. Type 2 DM treated with insulin	26	Semaglutide 3 mg oral qd	184	61 (9)	82 (44.6)	31.0 (6.8)	8.2 (0.7)	15.1 (7.9)	(1) HbA1C change
		Semaglutide 7 mg oral qd	182	60 (10)	79 (43.4)	31.1 (7.0)	8.2 (0.7)	16.2 (8.6)	(2) FPG, SMBG, achieve goal rate, time to rescue medication, BW, BMI, WC change, achieve goal rate, BP, HR, amylase, lipase, lipid profiles, EKG changes, AE, QoL
		Semaglutide 14 mg oral qd	181	61 (10)	96 (53.0)	30.8 (6.3)	8.2 (0.7)	14.1 (8.0)	
		Placebo	184	60 (10)	79 (42.9)	31.0 (6.5)	8.2 (0.7)	14.8 (7.9)	
Frøssing, 2018[15].	26	Liraglutide 1.8 mg/day sc qd	48	31.4 (24.6-35.6)	48 (100)	33.3 (5.1)	NR	NA	(1) Endogenous thrombin potential change (2) PAI-1, adrenomedullin, atrial natriuretic peptide, copeptin, hsCRP, bleeding ratio,

LIPT Phase 4 trial. PCOS		Placebo	24	26.2 (24.8-31.5)	24 (100)	33.3 (4.6)	NR	NA	percent liver fat, body composition, anti-müllerian hormone, ovarian volume change, BW
Rodbard, 2018[16] SUSTAIN™ 5 Phase 3 trial. Type 2 DM treated with insulin	30	Semaglutide 0.5 mg sc qw	132	59.1 (28-84)	58 (43.9)	32.8 (21.1-51.4)	8.4 (7.0-10.3)	12.9 (0.4-37.1)	(1) HbA1C change (2) SMBG, FPG change, achieve goal rate, insulin dose, BW change, BP, AE, satisfaction questionnaire
		Semaglutide 1 mg sc qw	131	58.5 (33-80)	54 (41.2)	32.0 (19.5-51.6)	8.3 (6.9-10.8)	13.7 (0.6-36.9)	
		Placebo qw	133	58.8 (19-86)	62 (46.6)	31.8 (21.0-48.8)	8.4 (6.8-11.1)	13.3 (0.8-39.6)	
Ishøy, 2017[17]. TAO Phase 3 trial. Obese, non-DM, schizophrenia	3 months	Exenatide 2 mg sc qw	20	37.4 (10.7)	9 (45)	39.5 (3.5)	5.2 (2.5)	NA	(1) BW change (2) Body fat composition
		Placebo qw	20	34.4 (10.6)	11 (55)	38.6 (6.3)	5.3 (2.6)		
Mensberg, 2017[18]. Phase 4 trial. Type 2 DM.	16	Liraglutide 1.8 mg/day sc qd	17	56.5 (9)	4 (24)	32.5 (3.7)	8.2 (1.4)	6.0 (5.2)	(1) HbA1C change (2) Glycemic control parameters, meal test, BW change, VO2peak, BP, EKG
		Placebo	16	55.6 (12)	6 (38)	32.4 (5.2)	8.0 (1.2)	3.7 (3.3)	
Sorli, 2017[19]	30	Semaglutide 0.5 mg sc qw	128	54.6 (11.1)	68 (53)	32.5 (7.6)	8.1 (0.9)	4.8 (6.1)	(1) HbA1C change (2) FPG change, achieve goal rate, BW, WC

SUSTAIN™ 1 Phase 3 trial. Drug-naïve type 2 DM		Semaglutide 1 mg sc qw	130	52.7 (11.9)	50 (38)	33.9 (8.4)	8.1 (0.8)	3.6 (4.9)	change, BP
		Placebo qw	129	53.9 (11.0)	59 (46)	32.4 (6.9)	8.0 (0.9)	4.1 (5.5)	
Blackman, 2016[20]. SCALE™ phase 3 trial. Obesity with OSA	32	liraglutide 3.0 mg/day sc qd	180	48.6 (9.9)	51 (28.3)	38.9 (6.4)	5.7 (0.4)	NA	(1) AHI change (2) BW, FPG, HbA1C change
		Placebo	179	48.4 (9.5)	50 (27.9)	39.4 (7.4)	5.6 (0.4)	NA	
Davies, 2016[21]. Phase 3 trial. Type 2 DM with CKD	26	Liraglutide 1.8 mg/day sc qd	140	68.0 (8.3)	65 (46.4)	33.4 (5.4)	8.1 (0.8)	15.9 (8.9)	(1) HbA1C change (2) SMPG change, achieve goal rate, BMI, eGFR change
		Placebo	137	66.3 (8.0)	72 (52.6)	34.5 (5.4)	8.0 (0.9)	14.2 (7.5)	
Dejgaard, 2016[22]. Phase 4 trial. Overweight type 1 DM	24	Liraglutide 1.8 mg/day sc qd	50	47 (13)	20 (40)	30.3 (3.5)	8.7 (0.7)	20 (12)	(1) HbA1C change (2) Glycemic excursions, BMI change, QoL, CV
		Placebo	50	49 (12)	15 (30)	29.8 (3.1)	8.7 (0.7)	25 (12)	
Kuhadiya, 2016[23]. Phase 3 trial. Type 1 DM	12	Liraglutide 0.6 mg/day sc qd	14	45 (4)	9 (64.3)	26 (3)	7.5 (0.2)	25 (2)	(1) Weekly glucose concentrations change (2) HbA1C, BW, total insulin dose change, AUC of glucose, acetaminophen concentration, carbohydrate intake, Insulin, C-peptide, incretin following meal
		Liraglutide 1.2 mg/day sc qd	16	42 (3)	5 (31.3)	33 (2)	7.8 (0.2)	21 (3)	
		Liraglutide 1.8 mg/day sc qd	16	42 (3)	11 (68.8)	28 (4)	7.4 (0.2)	20 (3)	

		Placebo	17	50 (3)	10 (58.8)	28 (2)	7.7 (0.2)	30 (3)	
Marso, 2016[24] SUSTAIN™Phase 3 trial). Type 2 DM and CVD	104	Semaglutide 0.5 mg sc qw	826	64.6 (7.3)	331 (40.1)	NR	8.7 (1.4)	14.3 (8.2)	(1) MACE (CV death, non-fatal MI, non-fatal stroke) (2) CV outcome, death, H bA1C, BW, FPG, lipid profiles, UACR change, BP, HR, lipid, AE, anti-semaglutide antibodies, PRO
		Semaglutide 1 mg sc qw	822	64.7 (7.1)	304 (37.0)		8.7 (1.5)	14.1(8.2)	
		Placebo 0.5 mg sc qw	824	64.8 (7.6)	342 (41.5)		8.7 (1.5)	14.0 (8.5)	
		Placebo 1 mg sc qw	825	64.4 (7.5)	318 (38.5)		8.7 (1.5)	13.2 (7.4)	
Nauck, 2016[25]. HARMONY 2 Phase 3 trial. Type 2 DM	52	Albiglutide 30 mg sc qw	101	53.6 (10.9)	43 (42.6)	33.7 (5.1)	8.0 (0.8)	3.4 (3.7)	(1) HbA1C change (2) Time to hyperglycemia rescue, FPG, BW, postprandial glucose change, achieve goal rate, Albiglutide concentration
		Albiglutide 50 mg sc qw	99	52.0 (11.8)	49 (49.5)	33.9 (5.5)	8.2 (0.9)	4.2 (4.6)	
		Placebo	101	53.1 (11.7)	43 (42.6)	33.0 (5.4)	8.0 (0.9)	4.3 (4.0)	
Vanderheiden, 2016[26]. Phase 4 trial. Type 2 DM/obesity	6 months	Liraglutide 1.8mg/day sc qd	35	52.8 (8.1)	23 (66)	40.7 (6.7)	9.0 (1.2)	16 (12-23)	(1) HbA1c change (2) TG content, BW change, Beta-Cell function, glucagon, insulin dose, number of daily injection, BP, lipid profiles, ae, liver function, QoL, Beta-cell function
		Placebo	36	55.5 (6.6)	22 (61)	41.6 (10.4)	8.9 (1.0)	18 (13-27)	
Ahmann, 2015[27]. Phase 3 trial. Type 2 DM with basal insulin	26	Liraglutide 1.8mg/day sc qd	225	59.3 (9.2)	105 (46.7)	32.3 (5.6)	8.2 (0.8)	12.1 (7.1)	(1) HbA1C change (2) FPG, SMBG, BW change, achieve goal rate, AE
		Placebo	225	57.5 (11.1)	89 (39.6)	32.2 (5.7)	8.3 (0.9)	12.1 (6.8)	

Davies 2015[28]. SCALE™ phase 3 trial. Obesity/ overweight type 2 DM	56	Liraglutide 3.0mg/day sc qd	423	55.0 (10.8)	203 (48.0)	37.1 (6.5)	7.9 (0.8)	7.5 (5.7)	(1) BW change (2) HbA1C, achieve goal rate, WC, BW changes, hypoglycemia
		Liraglutide 1.8mg/day sc qd	211	54.9 (10.7)	103 (48.8)	37.0 (6.9)	8.0 (0.8)	7.4 (5.2)	
		Placebo	212	54.7 (9.8)	103 (54.2)	37.4 (7.1)	7.9 (0.8)	6.7 (5.1)	
Retnakaran, 2014[29]. LIBRA Phase 3 trial. Type 2 DM	48	Liraglutide 6.0 mg/mL	26	58.9 (8.7)	10 (38.5)	30.0 (4.3)	6.4 (0.5)	3.0 (2- 5)	(1) Insulin Secretion-Sensitivity Index-2 (2) HbA1c, FPG change
		Placebo	25	57.4 (7.4)	9 (36)	30.4 (5.8)	6.2 (0.4)	1.5 (0.75-3)	
Kim, 2013[30]. Phase 3 trial. Pre-diabetes	14	Liraglutide 1.8mg/day sc qd	24	58 (7)	16 (67)	31.9 (2.7)	NR	NA	(1) BW change (2) Insulin AUC, insulin resistance after calorie restriction
		Placebo	27	58 (8)	17 (63)	31.9 (3.5)			
Wadden, 2013[31]. SCALE Maintenance phase 3 trial. Obese/ overweight	56	Liraglutide 3.0mg/day sc qd	212	45.9 (11.9)	84 (39.6)	36.0 (5.9)	5.6 (0.4)	NA	(1) BW change, achieve goal rate (2) BP, HR, lipid profiles, CVD marker, metabolic syndrome criteria, WC, BMI changes, glycemia control parameters
		Placebo	210	46.5 (11)	79 (37.6)	35.2 (5.9)	5.5 (0.4)	NA	

Continuous variables were presented with mean (standard deviation or range), categorical variables were presented with number (percentage)

^a Study period referred to the period of primary outcome assessed

^b Achieve goal rate in weight control referred to weight reduction >5%, 10, 20 % depending on studies

^b Achieve goal rate in diabetes control referred to glycated hemoglobin \leq 7 or 6.5 % depending on studies

Abbreviations: AE: Adverse events; AHI: Apnea-hypopnea index; AUC: Area under curve; AWARD-8: Study of How Dulaglutide Compares to Placebo in Participants With Type 2 Diabetes Who Are Also on Sulfonylurea Therapy; BMI: Body mass index; BP: Blood pressure; BW: Body weight; CKD: Chronic kidney disease; CRP: C-reactive protein; CV: Cardiovascular; CVD: Cardiovascular disease; DM, Diabetes mellitus; eGFR: Estimated Glomerular filtration rate; EKG: Electrocardiogram; FPG: Fasting plasma glucose; HbA1c: Glycated hemoglobin; HF: Heart failure; HOMA: Homeostatic model assessment; HR: Heart rate; hsCRP: High sensitivity C-reactive protein; ICOAP, Intermittent and Constant Osteoarthritis Pain questionnaire; KKOOS, Knee injury and Osteoarthritis Outcome Score; LIBRA, Liraglutide and Beta-cell RepAir; LIPT, Liraglutide in Polycystic Ovary Syndrome; LOSEIT, Liraglutide 3 mg for Knee Osteoarthritis; MACE: Major adverse cardiac events; MAGNA VICTORIA, Effect of Liraglutide on Cardiovascular Endpoints in Diabetes Mellitus Type 2 Patients of South Asian Descent; MI: Myocardial infarction; NA: Not-applicable; NR: Non-reported; OSA: Obstructive sleep apnea; PAI-1: Plasminogen activator inhibitor-1 activity; PIONEER 1: Efficacy and Safety of Oral Semaglutide Versus Placebo in Subjects With Type 2 Diabetes Mellitus Treated With Diet and Exercise Only; PIONEER 5: Efficacy and Safety of Oral Semaglutide Versus Placebo in Subjects With Type 2 Diabetes and Moderate Renal Impairment; PIONEER-6: A Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes; PIONEER 8: Efficacy and Safety of Oral Semaglutide Versus Placebo in Subjects With Type 2 Diabetes Mellitus Treated With Insulin; PRO: Patient reported outcome; REWIND: Researching Cardiovascular Events With a Weekly Incretin in Diabetes; sc: Subcutaneous; SMBG: Self-monitoring of blood glucose; STEP 1: Research Study Investigating How Well Semaglutide Works in People Suffering From Overweight or Obesity; STEP 2: Research Study Investigating How Well Semaglutide Works in People With Type 2 Diabetes Suffering From Overweight or Obesity; STEP 3: Research Study to Look at How Well Semaglutide is at Lowering Weight When Taken Together With an Intensive Lifestyle Program; SUSTAIN™ 1: Efficacy and Safety of Semaglutide Once-weekly Versus Placebo in Drug-naïve Subjects With Type 2 Diabetes; SUSTAIN™ 5: Efficacy and Safety of Semaglutide Once-weekly Versus Placebo as add-on to Basal Insulin Alone or Basal Insulin in Combination With Metformin in Subjects With Type 2 Diabetes; SUSTAIN™ 6: Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes; TAO: Treatment of Antipsychotic-associated Obesity With a GLP-1 Analogue; TG: Triglyceride; QoL: Quality of Life; Qw: Once per week; UACR: Urinary albumin to creatinine ratio; VAT: Visceral adipose tissue; VO₂peak: Maximal oxygen uptake; WOMAC, Western Ontario and McMaster Universities Arthritis Index; WC: Waist circumference

Reference

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