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Research article

A meta-analysis preliminary result: Effectiveness and Safety of Oral Semaglutide vs. Injectable Semaglutide in Weight Loss in General Population Indifferent of Diabetic Status

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ABSTRACT

Background: Semaglutide, a well-known medication used in treating type 2 Diabetes Mellitus, has gained attention for its beneficial effects on weight loss, leading to its investigation for use in obesity management. The US Food and Drug Administration recently approved a glucagon-like peptide-1 receptor agonist for chronic weight management. Semaglutide is the only drug among GLP-1RAs available in injectable and oral forms for treating diabetes. However, its approval for obesity treatment is limited to subcutaneous injection.

Methods: This study aims to conduct a meta-analysis comparing the efficacy and safety of oral and injectable forms of Semaglutide in overweight patients. PubMed, Medline, Web of Science, the Cochrane Library, Embase, Google Scholar, and CINAHL databases were systematically searched. Comprehensive Meta-Analysis version 3 was utilized for statistical analysis.

Results: A total of 20 eligible articles published between 2015 and 2023 were included, comprising 7,852 participants (4,525 in the Semaglutide group and 3,327 in the placebo group). Seventeen studies utilized subcutaneous Semaglutide, while five studies evaluated the oral form. Analysis was conducted on the overall efficacy of Semaglutide, with subsequent sub-analysis comparing oral versus injectable forms, high-dose versus low-dose, diabetic versus non-diabetic patients, and the general population versus specific comorbidities. Additionally, side effects of oral versus injectable forms were assessed.

Conclusion: Overall, our findings contribute to the understanding of Semaglutide's effectiveness and safety profile in managing obesity, providing insights into potential differences between oral and injectable formulations.

KEYWORDS Semaglutide, glucagon-like peptide-1 receptor agonist (GLP-1 agonist), type 2 Diabetes mellitus (DM), obesity, subcutaneous semaglutide, oral semaglutide.

INTRODUCTION

Semaglutide, a medication approved by the US Food and Drug Administration for chronic weight management, is a glucagon-like peptide-1 receptor agonist (GLP-1RA) [1]. It has demonstrated effectiveness in reducing weight and improving blood sugar and lipid levels [2]. Unlike other GLP-

1RAs available only as subcutaneous injections, Semaglutide is unique as it also comes in an oral form. While both forms are approved for treating type 2 diabetes in the United States, only the injectable version is approved for obesity treatment [3]. The recommended dose for weight management is a weekly subcutaneous injection of 2.4 mg, taken consistently on the same day each week, with or without meals [4]. The most commonly reported adverse effects of Semaglutide are gastrointestinal, such as nausea, diarrhea, and vomiting [2]. The comparative efficacy and safety of oral versus injectable Semaglutide specifically for obesity treatment have not been systematically reviewed. Therefore, this meta-analysis aims to evaluate Semaglutide's effectiveness in promoting weight loss, compare oral and injectable Semaglutide treatments in obese individuals regardless of diabetes or heart disease status, and assess the impact of different doses of Semaglutide. Additionally, it will examine and compare reported side effects between oral and injectable interventions.

METHODS

Search strategy

A systematic search was conducted on PubMed, Medline, Web of Science, the Cochrane Library, Embase, Google Scholar and CINAHL from database inception until January 2024 to look for potentially eligible articles. The search strategy was based on the following key search terms: "Semaglutide" AND "weight loss" OR "body weight" OR "obesity" OR "overweight". All retrieval processes were performed independently by two researchers.

Selection Criteria

Relevant articles were screened by title and abstract after removing duplicates. Studies were eligible for inclusion if they addressed the effectiveness and safety of Semaglutide in weight loss. The remaining studies were then examined in full text to confirm eligibility.

Inclusion criteria for articles were: (1) randomized controlled trial reporting the efficacy and safety of Semaglutide in weight loss; (2) studies that used placebo as comparator group; (3) publications reporting sufficient data to establish the mean difference in body weight (Kg) change from baseline between Semaglutide and placebo groups; and (4) studies published as original articles. Exclusion criteria were: (1) no full text electronically available; (2) publication in a language other than English; (3) observational studies, comments, letters, editorials, protocols, guidelines, and review papers; and (4) studies with insufficient outcome data.

Outcome

- The mean difference in body weight (Kg) change from baseline between Semaglutide and placebo groups.
- The safety was assessed by the incidence of serious adverse events between Semaglutide and placebo groups.

Data extraction

Two independent authors retrieved information from the eligible articles following the inclusion and exclusion criteria. Information was collected on a standardized data sheet that included: (1) Study ID (name of first author, year of publication), (2) trial, (3) country, (4) study population, (5) Mean age (SD), years, (6) gender, M/F (7) BMI, kg/m^2, (8) intervention, (9) control group, (10) sample size, Semaglutide/placebo, and (11) study duration, weeks.

Quality assessment of studies

Using the Cochrane Risk of Bias Assessment Tool criteria, two investigators independently evaluated the risk of bias for the included studies using Review Manager 5.4.1 software. This tool covered the risk of bias in five different areas: selection bias, performance bias, detection bias, attrition bias, and reporting bias. The risk of bias was classified into three levels: high, low, and unclear. When there were variations in the data assessment, a third investigator reconciled the disparities.

Statistical Analysis

The statistical analyses were performed using Comprehensive Meta-Analysis version 3 (Biostat Inc. USA). The mean difference (MD) in body weight change from baseline between Semaglutide and placebo groups with 95% confidence intervals (CIs) was calculated to evaluate the efficacy of Semaglutide in weight loss. The Odds Ratio (OR) with 95% confidence intervals (CIs) was calculated to evaluate the incidence of serious adverse events between Semaglutide and placebo groups. A value of $p < 0.05$ was considered as the level of significance. The Cochrane *chi*-squared test was used to evaluate heterogeneity among articles, with a p-value < 0.05 indicating the existence of heterogeneity. To estimate the impact of heterogeneity on the meta-analysis, I^2 value was calculated. I^2 values $\geq 50\%$ and $p < 0.05$ indicated a moderate to high heterogeneity among pooled studies. A fixed-effects design was used when $I^2 < 50\%$ and $p > 0.05$; otherwise, a random-effects model was adopted [5]. We also performed a subgroup analysis to assess the efficacy of Semaglutide in weight loss across different groups. Egger's test was conducted to evaluate publication bias. This latter was further assessed by the visual inspection of the symmetry in funnel plots.

RESULTS

Identification of studies

The database search identified 1046 studies to be screened, of which 351 abstracts were identified as potentially eligible and retrieved for full-text review. Eligibility criteria were met by 20 articles, which were included in this systematic review and meta-analysis study. The PRISMA flowchart is shown in Figure 1.

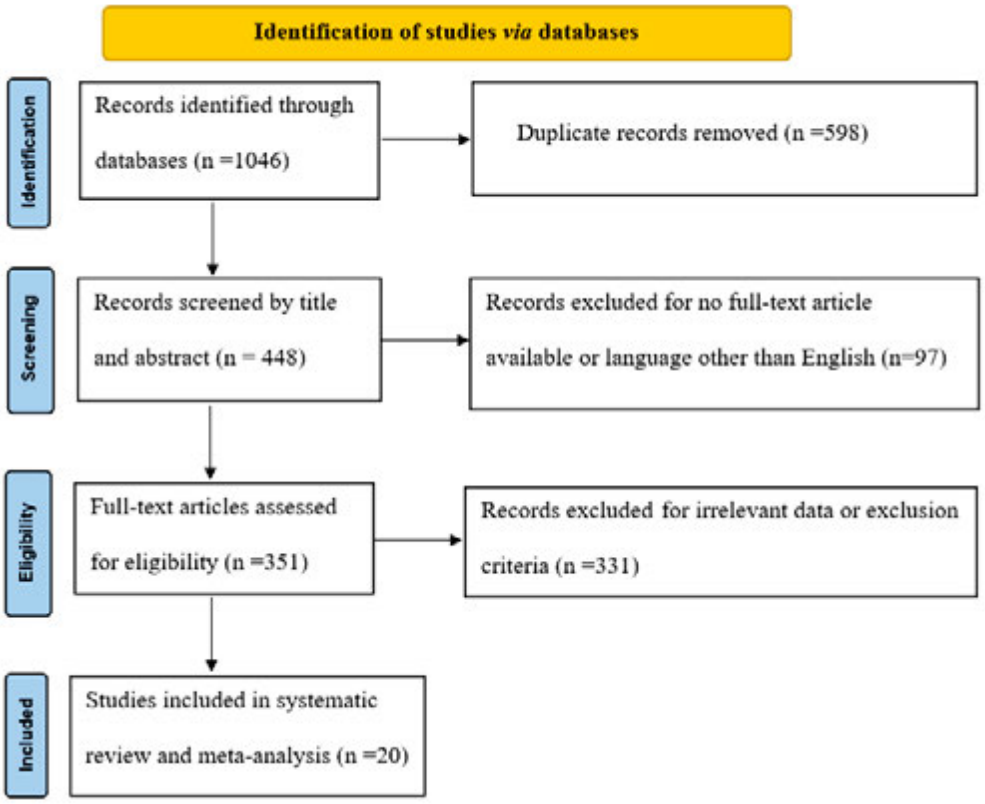

FIGURE 1. PRISMA flow diagram.

Characteristics of included studies

The included articles were published between 2015 and 2023. Eight studies investigated the efficacy of Semaglutide among patients with obesity, while seven studies investigated the efficacy of Semaglutide among patients with T2D. The sample size of the included articles was 7852 participants, with 4525 participants in the Semaglutide group and 3327 in the placebo group. The mean age (SD) of participants varied between 15.4 (1.5) and 70 (8). The BMI (SD) ranged from 21.95 kg/m^2 to 40 (8) kg/m^2. Subcutaneous Semaglutide was used by 17 studies, while oral Semaglutide was used by 5 studies, and the dose of Semaglutide varied between 2.5 mg to 50 mg for oral Semaglutide and 0.4 mg to 2.4 mg for subcutaneous Semaglutide. In this meta-analysis, we selected data of the highest concentration of Semaglutide in studies that reported different concentrations. The study duration ranged from 12 to 72 weeks. The characteristics of included studies are summarized in Table 1.

Risk of bias assessment

Overall, the risks of bias were relatively low for the whole included trials. According to the Cochrane Risk of Bias Assessment Tool, all the trials were double-blinded and randomized, using an interactive web-based response system with an identically looking placebo and Semaglutide. Hence, they are at low risk for selection, detection, and performance biases. However, four studies were rated as high risk of bias in terms of incomplete outcome data because data for those who were lost to follow-up were included, which could affect the mean weight difference. In terms of other risks of bias, the majority of studies were rated as unclear risks because they had confounding factors such as diet that may have significantly affected the magnitude of weight loss (Figure 2).

Body weight change from baseline

Twenty studies assessed the mean difference (MD) in body weight change from baseline between Semaglutide and placebo groups. We used a random-effects design due to the high heterogeneity (Chi^2 = 1230868.76, p = 0.000, I^2 = 99%). The forest plot analysis found that Semaglutide led to a significantly higher reduction from baseline in mean body weight compared to placebo (MD: -10.097; 95% CI: -10.104--10.090; p = 0.000) (Figure 3).

Subgroups analysis

We also analyzed subgroups for the study population, including patients with obesity, followed by patients with Nonalcoholic steatohepatitis, patients with obesity and heart failure, patients with obesity and T2D, healthy patients, and finally, patients with T2D. Another subgroup, the type of drug, was also compared to analyze the mean difference in

FIGURE 2. (A) Risk of bias summary: review authors' judgments about each risk of bias item for each included study. (B) Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Blundell et al. 2017	-6,000	0,037	0,001	-6,072	-5,928	-164,317	0,000
Davies et al. 2017 (O)	-0,900	0,092	0,008	-1,080	-0,720	-9,799	0,000
Davies et al. 2017 (S)	-5,200	0,095	0,009	-5,386	-5,014	-54,929	0,000
Davies et al. 2021	-6,180	0,028	0,001	-6,235	-6,125	-219,450	0,000
Friedrichsen et al. 2020	-10,000	1,136	1,290	-12,226	-7,774	-8,804	0,000
Garvey et al. 2022	-12,900	0,127	0,016	-13,148	-12,652	-101,816	0,000
Ikushima et al. 2018 (J)	-6,100	0,054	0,003	-6,206	-5,994	-112,950	0,000
Ikushima et al. 2018 (C)	-8,200	0,108	0,012	-8,412	-7,988	-75,917	0,000
Kadowaki et al. 2022	-9,510	0,012	0,000	-9,534	-9,486	-778,408	0,000
Knop et al. 2023	-13,000	0,039	0,001	-13,076	-12,924	-335,742	0,000
Kosiborod et al. 2023	-11,200	0,035	0,001	-11,268	-11,132	-321,995	0,000
Mosenzon et al. 2019	-2,600	0,011	0,000	-2,622	-2,578	-233,996	0,000
Nauck et al. 2015	-3,600	0,021	0,000	-3,641	-3,559	-173,576	0,000
Newsome et al. 2020	-11,470	0,016	0,000	-11,501	-11,439	-729,891	0,000
O'Neil et al. 2018	-12,670	0,113	0,013	-12,892	-12,448	-111,927	0,000
Pratley et al. 2019	-3,300	0,021	0,000	-3,340	-3,260	-160,634	0,000
Rodbard et al. 2018	-5,000	0,025	0,001	-5,048	-4,952	-203,095	0,000
Sorli et al. 2017	-3,550	0,050	0,002	-3,647	-3,453	-71,414	0,000
Wadden et al. 2021	-10,600	0,026	0,001	-10,650	-10,550	-411,885	0,000
Weghuber et al. 2022	-17,700	0,030	0,001	-17,759	-17,641	-591,473	0,000
Wilding et al. 2021	-12,700	0,005	0,000	-12,709	-12,691	-2652,511	0,000
Zinman et al. 2019	-4,200	0,021	0,000	-4,241	-4,159	-200,595	0,000
	-10,097	0,004	0,000	-10,104	-10,090	-2827,814	0,000

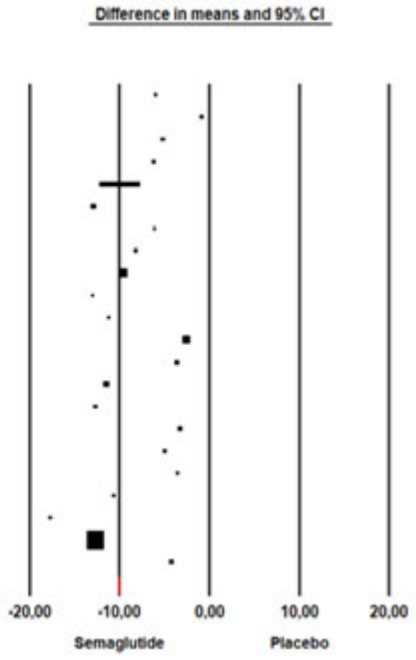

FIGURE 3. Forest plot showing the estimated mean difference in body weight between Semaglutide and placebo.
(O: Oral, S: subcutaneous, J: Japanese, C: Caucasian)

body weight change from baseline between subcutaneous Semaglutide and oral Semaglutide. Subgroup analysis was also performed according to the dose of the drug. The results will be published in full in the next release.

Safety

Eighteen studies assessed the prevalence of serious adverse events between Semaglutide and placebo groups. We used a random-effects design due to the high heterogeneity and the forest plot analysis. The full results will be released later on.

Publication bias

We will conduct the funnel plot asymmetry test to assess the potential publication bias of included studies. The result will be published in full later on.

DISCUSSION

The MD of -10.097 indicates that, on average, individuals treated with Semaglutide experienced a weight reduction of 10.097 units more than those who received a placebo. The CI, ranging from -10.104 to -10.090, suggests that in 95% of similar studies, the actual mean difference would fall within this interval. Furthermore, the *p*-value of 0.000 indicates that the mean body weight reduction difference between the Semaglutide and placebo groups is statistically significant.

CONCLUSION

We examined 20 randomized controlled trials to compare the impact of Semaglutide on weight loss. Overall, our preliminary findings suggest that Semaglutide is associated with a significantly higher reduction in mean body weight compared to placebo, supported by both the magnitude of the mean difference and the statistical significance indicated by the *p*-value. Further results are necessary to confirm these findings.

CONFLICTS OF INTEREST

None of the authors have conflicts of interest to declare.

TABLE 1: **Characteristics of studies included in the meta-analysis.**

Study ID	Trial	Country	Study population	Mean age, years (SD)	Gender, M/F	BMI, kg/m^2	Intervention	Sample size, Semaglutide/ placebo	Study duration, weeks
Blundell et al. 2017 [6]	A single-center, randomized, double-blind, placebo-controlled, two-period crossover trial	UK	Eligible subjects were $\geq$ 18 years of age, with a body mass index (BMI) of 30 to 45 kg/m^2, HbA1c < 6.5% and stable body weight (< 3 kg change during the 3 months prior to screening)	42	20/10	33.8	Subcutaneous Semaglutide: 1 mg (once a week)	15/15	12
Davies et al. 2017 [7]	Randomized, parallel-group, phase 2, dosage finding trial	14 countries	Patients (18 years or older) with type 2 diabetes and insufficient glycemic control (HbA1c level range, 7.0%-9.5%) on diet and exercise alone or with a stable dose (at least 30 days) of metformin	57.5 (10.6)	133/77	31.6 (4.2)	- Oral Semaglutide: 2.5 mg (once a day) - Subcutaneous Semaglutide: 1 mg (once a week)	70 (O), 69 (S)/71	26
Davies et al. 2021 [8]	A randomized, double-blind, double-dummy, placebo-controlled, phase 3 trial (STEP 2)	12 countries across Europe, North America, South America, the Middle East, South Africa, and Asia	Participants were 18 years or older, reported at least one unsuccessful dietary effort to lose weight, had a body-mass index of at least 27 kg/m^2, HbA1c of 7–10% (53–86 mmol/mol), and had been diagnosed with type 2 diabetes at least 180 days before screening	55 (11)	394/413	35.9 (6.4)	Subcutaneous Semaglutide: 2·4 mg (once a week)	403/404	68
Friedrichsen et al. 2020 [9]	Single-center, randomized, double-blind, placebo-controlled, parallel-group, phase 1 trial	Germany	Participants were men and women, aged 18 to 65 years, with body mass index (BMI) of 30.0 to 45.0 kg/m^2	42.8 (11.1)	44/28	34.4 (3.0)	Subcutaneous Semaglutide: 2·4 mg (once a week)	36/36	20

Study ID	Trial	Country	Study population	Mean age, years (SD)	Gender, M/F	BMI, kg/m^2	Intervention	Sample size, Semaglutide/ placebo	Study duration, weeks
Garvey et al. 2022 [10]	Phase 3, randomized, double-blind, placebo-controlled, multinational trial (STEP 5)	Canada, Italy, Hungary, Spain, and the United States	Participants were aged $\geq$ 18 years at the time of signing informed consent. BMI $\geq$ 30.0 kg/m^2 or $\geq$ 27.0 kg/m^2 with the presence of at least one of the following weight-related comorbidities (treated or untreated): hypertension, dyslipidemia, obstructive sleep apnea or cardiovascular disease	47.3 (11.0)	68/236	38.5 (6.9)	Subcutaneous Semaglutide: 2·4 mg (once a week)	152/152	104
Ikushima et al. 2018 [11]	A clinical pharmacology, single-center, parallel-group, randomized, double-blind, placebo-controlled trial	Japan	Healthy male subjects, age 20–55 years, with good glycemic control [HbA1c 6.0% (42 mmol/mol) or less]; body mass index (BMI) in the range of 20–25 kg/m^2 with the body weight of at least 54 kg; and with both parents either Japanese (for Japanese subjects) or Caucasian (for Caucasian subjects) were eligible for inclusion	38	28 men	21.95	Subcutaneous Semaglutide: 1.0 mg (once a week)	- 8/6 (Japanese participants) - 8/6 (Caucasian participants)	13
Kadowa-ki et al. 2022 [12]	A randomized, double-blind, double-dummy, placebo-controlled, phase 3a trial (STEP 6)	Japan and South Korea	Adults (aged $\geq$ 18 years in South Korea; $\geq$ 20 years in Japan) with a BMI of at least 27·0 kg/m^2 with two or more weight-related comorbidities or a BMI of 35·0 kg/m^2 or more with one or more weight-related comorbidity (one comorbidity had to be either hypertension, dyslipidemia, or, in Japan only, type 2 diabetes) who had at least one self-reported unsuccessful dietary attempt to lose bodyweight	51 (10.5)	189/111	31.9 (4.4)	Subcutaneous Semaglutide: 2.4 mg (once a week)	199/101	68

Study ID	Trial	Country	Study population	Mean age, years (SD)	Gender, M/F	BMI, kg/m^2	Intervention	Sample size, Semaglutide/ placebo	Study duration, weeks
Knop et al. 2023 [13]	A randomized, double-blind, placebo-controlled, phase 3 trial (OASIS 1)	9 countries across east Asia, Europe, and North America	Participants who were aged 18 years or older (aged 20 years or older in Japan per Japanese regulatory requirements), with a BMI of at least 30 kg/m^2, or at least 27 kg/m^2 with one or more bodyweight-related complications or comorbidities (hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease), and with at least one self-reported dietary bodyweight loss effort was eligible	50 (13)	182/485	37.5 (6.5)	Oral Semaglutide: 50 mg (once a day)	334/333	68
Kosibor-od et al. 2023 [14]	A randomized, double-blind, placebo-controlled trial	13 countries in Asia, Europe, and North and South America	Persons 18 years of age or older were eligible to participate if they had a left ventricular ejection fraction of at least 45%; a body-mass index of at least 30	69	232/297	37	Subcutaneous Semaglutide: 2.4 mg (once a week)	263/266	52
Mosenz-on et al. 2019 [15]	Multicentre, double-blind, randomised, placebo-controlled, phase 3a trial (PIONEER 5)	Denmark, Finland, Israel, Poland, Russia, Sweden, the UK, and the USA	Patients were aged 18 years or older, with type 2 diabetes (diagnosed $\geq$ 90 days before screening), had a HbA1c of 7·0–9·5% (53–80 mmol/mol) and moderate renal impairment (chronic kidney disease-Epidemiology Collaboration [CKD-EPI] stage 3), defined as an eGFR of 30–59 mL/min per 1·73 m^2, calculated by use of the CKD-EPI formula).	70 (8)	156/168	32.4 (5.4)	Oral Semaglutide: 14 mg (once a day)	163/161	26

Study ID	Trial	Country	Study population	Mean age, years (SD)	Gender, M/F	BMI, kg/m^2	Intervention	Sample size, Semaglutide/ placebo	Study duration, weeks
Nauck et al. 2015 [16]	Randomized, nine-armed, parallel-group, phase 2, dose-finding trial, which was double-blind	14 countries (Austria, Bulgaria, Finland, France, Germany, Hungary, India, Italy, Serbia, South Africa, Spain, Switzerland, Turkey, and the U.K.)	Patients ≥ 18 years of age who had received a diagnosis of type 2 diabetes, and had been treated with either diet and exercise alone or together with a stable regimen of metformin monotherapy ($1,500 mg) for at least 3 months were enrolled	55.8 (10.5)	52/41	31.3 (4.25)	Subcutaneous Semaglutide: 1.6 mg (once a week)	47/46	12
Newsome et al. 2020 [17]	Randomized, double-blind, placebo-controlled, parallel-group trial	16 countries	Patients were 18 to 75 years of age, with or without type 2 diabetes, and had a body-mass index of greater than 25 at screening. Additional key inclusion criteria were histologic evidence of NASH and an activity score for nonalcoholic fatty liver disease of 4 or higher	53.3 (10.5)	71/91	35.6 (6.6)	Subcutaneous Semaglutide: 0.4 mg (once a day)	82/80	72
O'Neil et al. 2018 [18]	A randomized, double-blind, placebo and active-controlled, dose-ranging, phase 2 trial	Australia, Belgium, Canada, Germany, Israel, Russia, UK, and USA	Participants were adults who were 18 years or older without diabetes, and with a body-mass index (BMI) of 30 kg/m^2 or more	47 (13)	84/154	40 (8)	Subcutaneous Semaglutide: 0.4 mg (once a day)	102/136	52
Pratley et al. 2019 [19]	A randomized, double-blind, double-dummy, active-controlled, and placebo-controlled phase 3a trial (PIONEER 4)	Croatia, Czech Republic, Germany, Hungary, Japan, Latvia, Poland, Slovakia, South Africa, Ukraine, United Arab Emirates, and the USA	Patients were aged 18 years or older with type 2 diabetes and HbA1c of 7·0–9·5% (53–80·3 mmol/mol), on a stable dose of metformin (≥ 1500 mg or maximum tolerated)	56.5 (10)	221/206	32.7 (6)	Oral Semaglutide: 14 mg (once a day)	285/142	52

Study ID	Trial	Country	Study population	Mean age, years (SD)	Gender, M/F	BMI, kg/m^2	Intervention	Sample size, Semaglutide/ placebo	Study duration, weeks
Rodbard et al. 2018 [20]	Randomized, double-blind, placebo-controlled, parallel-group, multinational, multicenter, four-armed trial (SUSTAIN 5)	Germany, Japan, Serbia, Slovakia, and the United States	Patients were ≥ 18 years of age and diagnosed with T2D	58.6	148/116	31.9	Subcutaneous Semaglutide: 1.0 mg (once a week)	131/133	30
Sorli et al. 2017 [21]	A phase 3a, randomized, double-blind, parallel-group, multinational, multi-center trial (SUSTAIN 1)	Canada, Italy, Japan, Mexico, Russia, South Africa, UK, and USA	Participants were adults aged 18 years or older with type 2 diabetes treated with diet and exercise alone for at least 30 days before screening when enrolled and an HbA1c of 7·0%–10·0% (53–86 mmol/mol)	53.3 (11.45)	150/109	33.16 (7.64)	Subcutaneous Semaglutide: 1.0 mg (once a week)	130/129	30
Wadden et al. 2021 [22]	Randomized, double-blind, placebo-controlled, multicenter study (STEP 3)	USA	Participants were aged 18 years or older, reported 1 or more unsuccessful dietary efforts to lose weight, and had either body mass index (BMI) of 27 or higher	46 (13)	116/495	37.9 (6.8)	Subcutaneous Semaglutide: 2.4 mg (once a week)	407/204	68
Weghub-er et al. 2022 [23]	Multinational, double-blind, parallel-group, randomized, placebo-controlled, phase 3a clinical trial	ND	Eligible participants were adolescents (12 to < 18 years of age) with a BMI in the 95th percentile or higher or with overweight (a BMI in the 85th percentile or higher)	15.4 (1.5)	76/125	36.7 (6.0)	Subcutaneous Semaglutide: 2.4 mg (once a week)	134/67	68

Study ID	Trial	Country	Study population	Mean age, years (SD)	Gender, M/F	BMI, kg/m^2	Intervention	Sample size, Semaglutide/ placebo	Study duration, weeks
Wilding et al. 2021 [2]	A randomized, double-blind, placebo-controlled trial	16 countries in Asia, Europe, North America, and South America	Adults (18 years of age or older) with one or more self-reported unsuccessful dietary efforts to lose weight and either a BMI of 30 or greater or a BMI of 27 or greater with one or more treated or untreated weight-related coexisting conditions (i.e., hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease)	46.5 (12.5)	508/1453	37.9 (6.6)	Subcutaneous Semaglutide: 2.4 mg (once a week)	1306/655	68
Zinman et al. 2019 [24]	Randomized, double-blind, placebo-controlled, parallel-group trial (PIONEER 8)	9 countries	Adult patients with type 2 diabetes diagnosed $\geq$ 90 days before screening with baseline HbA1c 7.0–9.5% (53–80 mmol/mol) were enrolled	60.5 (10)	190/175	30.9 (6.4)	Oral Semaglutide: 14 mg (once a day)	181/184	52

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