# Efficacy and safety of semaglutide in type 2 diabetes compared with sitagliptin, exenatide ER, insulin glargine, basal insulin and placebo: a systematic review

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**ABSTRACT**

Type 2 diabetes mellitus (T2DM) is a worldwide metabolic disorder associated with various complications. Despite available treatments for T2DM, there is still a significant unmet medical requirement. Recently, there is a new anti-diabetic drug namely once-weekly glucagon-like peptide 1 receptor agonist (GLP-1 RA), for example, semaglutide and duraglutide. This article will discuss the drug, semaglutide, in term of efficacy and safety. The purpose of this paper was to review efficacy and safety profiles of semaglutide. The relevant English-language articles were identified from PubMed, Web of Science, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, American Diabetes Association (ADA) meeting and European Association for the Study of Diabetes (EASD) meeting. Search items were semaglutide, diabetes mellitus [MeSH], glucose-like peptide 1 receptor agonists. Randomized controlled trials (RCTs) contain efficacy parameters (glycosylated hemoglobin [HbA1c, A1C], fasting plasma glucose [FPG], body weight [BW]) and safety parameters (incidence of hypoglycemia, retinopathy, nausea) were selected. Seven phase 3 RCTs were included. Semaglutide provided superior glycemic control compared with other glucose lowering drugs, supported by higher mean reduction of HbA1c, FPG and BW. Incidence of blood-confirmed or severe hypoglycemia of semalgutide was lower than others. However, incidence of nausea in semaglutide treatment was more than other comparators. In addition, incidence of diabetic retinopathy of semaglutide was similar to sitagliptin and insulin glargine, but more than placebo. Compared with other glucose lowering medications, semaglutide showed promising results in term of the reduction of HbA1c, BW, FPG, lower incidence of hypoglycemia, and comparable incidence of nausea and diabetic retinopathy.

## 1. INTRODUCTION

It is estimated that 415 million people have diabetes worldwide[1]. It is expected to rise to 592 million in 2035[2]. Diabetes mellitus is not only chronic disease, but also brings a variety of complications, such as diabetic retinopathy.

The glucagon-like peptide 1 receptor agonists (GLP-1 RAs) mimic the effects of endogenous GLP-1 hormone, stimulate insulin secretion and suppress glucagon secretion (in a glucose-dependent manner). GLP-1 RAs manage glycemic condition and stimulate satiety, as a result reducing food intake and body weight[3]. Currently, there are two types of GLP-1 RAs namely short-acting (such as exenatide, lixisenatide) and long-acting (such as liraglutide, dulaglutide, semaglutide) for the treatment of type 2 diabetes mellitus (T2DM).

Subcutaneous semaglutide is a new

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once-weekly GLP-1 RA. Through the modification of amino acid in position 8, spacer and C-18 fatty di-acid chain at position 26, it increases the half-life of semaglutide (~165 hours) compared with once-daily liraglutide (~12 hours)[4]. Semaglutide not only inhibits gastric emptying and activates peripheral vagal nerve, but also induces satiety through homeostasis and hedonic (emotional) pathways including effects on hindbrain, hypothalamus and mesolimbic region[5-6]. Several clinical trials have been conducted to evaluate the effect of sema-glutide.

Recently, the new oral form of semaglutide is introduced. Oral semaglutide employs sodium N-(8-(2-hydroxybenzoyl) amino) caprylic acid (SNAC) technique[7]. SNAC forms non-covalent interaction with semaglutide, and protects it from chemical barriers then by using passive transcellular manner to improve absorption of semaglutide through intestine into bloodstream[8]. Phase 2 study revealed that oral semaglutide once-daily (2.5 mg – 40 mg) reduces HbA1c and body weight in T2DM. In addition, oral semaglutide had similar safety and toler-ability findings compared with once-weekly subcutaneous semaglutide[9-10].

The objective of this article was to systematically review efficacy and safety of semaglutide compared with other glucose-lowering drugs or placebo.

## 2. MATERIALS AND METHODS

### 2.1. Study design

This study was a systematic review that followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[11]. This review focused on anti-diabetic effects of semaglutide in type 2 diabetes. We searched the following data-bases: PubMed, Web of Science, Cochrane Central Register of Controlled Trials, Clinical Trials.gov, American Diabetes Association (ADA) meeting, and European Association for the Study of Diabetes (EASD) meeting

to obtain the related studies.

### 2.2. Search strategy

The above-mentioned databases in study design were searched from inception until end of July 2017. The search strategy was based on a single search keyword or a broad combined search strings as below: GLP-1 RAs, diabetic mellitus [MeSH], glucose control, and randomized controlled trials, these terms were followed by sema-glutide. Articles were limited to English language and human.

### 2.3. Inclusion criteria

Studies eligible for this systematic review were performed on the basis of the following inclusion criteria: a) RCTs of semaglutide comparing with other anti-diabetic medications or placebo. b) Studies' participants were type 2 diabetes patients. c) The duration of study were at least 6 months. d) The outcomes of efficacy were provided such as HbA1c (A1C), fasting plasma glucose (FPG), and body weight (BW). e) Safety outcomes were monitored.

### 2.4. Exclusion criteria

If articles were not in English language, they were excluded.

### 2.5. Data extraction and analysis

Firstly, screened the articles according to titles, and then abstracts, finally full-text articles. Standardized predefined forms extracted data (such as study acronym, author, year of publication, diabetes duration, treat-ment duration, comparators, average age of participants, baseline treatment) from eligible studies. Quality of study and methodology were assessed through the items in the Cochrane risk-of-bias tool[12] (such as random sequence generation, allocation concealment, blinding of participants and personnel and outcome assessment, and incomplete data and selective reporting).

*Efficacy and safety of semaglutide in type 2 diabetes compared with sitagliptin,*
*exenatide ER, insulin glargine, basal insulin and placebo: a systematic review*

125

## 3. RESULTS

### 3.1. Study characteristics

We found 251 articles, 180 articles remained after duplicated removed. We subsequently screened by title and abstracts and 11 full-text articles were remaining. After reviewing the full-text, seven RCTs were eligible in this systematic review. Seven RCTs had a total of 7,516 participants with type 2 diabetes and the study duration was from 30 to 104 weeks (Table 1).

**Table 1.** Characteristics of included studies

| Study Acronym | Author, year | Study design | Inclusion criteria | Comparator | Male/ female, % | Diabetes duration, year | Age, year* | A1C, %* | FPG, mmol/L | BW, kg |
|---|---|---|---|---|---|---|---|---|---|---|
| SUSTAIN 1 | Sorli et al., 2017[13] | R, DB, PC, 30 weeks N=388 (2:2:1:1) | T2DM Age ≥ 20 A1C 7.0-10.0% Diet and exercise alone | Placebo | 54.0/46.0 | 4.18 | 53.7 | 8.05 | NA | 91.93 |
| SUSTAIN 2 | Ahrén et al., 2017[14] | R, DB, DD, AC, 56 weeks N=1225 (2:2:1:1) | T2DM Age ≥ 20 Met or Pio or Ros or any combination A1C 7.0-10.5% | Sitagliptin 100 mg | 51.0/49.0 | 6.57 | 55.1 | 8.07 | 9.60 | 89.30 |
| SUSTAIN 3 | Ahmann et al., 2016[15] | R, OL, AC, 56 weeks N=813 (1:1) | T2DM 1-2 OADs (Met, SU, TZDs) A1C 7.0-10.5% | Exenatide ER 2.0 mg | NA | 9.20 | 56.6 | 8.30 | 10.5 | 95.80 |
| SUSTAIN 4 | Aroda et al., 2017[16] | R, OL, AC, 30 weeks N=1089 (1:1:1) | T2DM Age ≥ 18 Met ± SU A1C 7.0-10.0% | Insulin glargine | 53.0/47.0 | 8.60 | 56.5 | 8.20 | 9.70 | 93.50 |
| SUSTAIN 5 | Robard et al., 2016[17] | R, DB, PC, 30 weeks N=397 (2:2:1:1) | T2DM Age ≥ 20 Basal insulin^ ± Met A1C 7.0-10.0% | Basal insulin | NA | 13.30 | NA | 8.40 | 8.60 | 91.70 |
| SUSTAIN 6 | Steven et al., 2016[6] | R, DB, PC, 104 weeks N=2735 (1:1:1:1) | T2DM Age≥50 with CVD Age ≥ 60 with subclinical CVD Insulin ± 1-2 OADs A1C ≥ 7.0% | Placebo | 60.7/39.3 | 13.90 | 64.6 | 8.70 | NA | 92.10 |
| SUSTAIN™ | Seino et al., 2017[18] | R, OL, AC, 30 weeks N=308 (1:1:1) | T2DM Age ≥ 20 A1C 6.5-10.5% OAD monotherapy | Sitagliptin, 100 mg | 76.3/23.7 | 8.00 | 58.3 | 8.10 | 9.30 | 69.30 |

*When not reported for the overall population, values have been estimated as weighted means. "NA" = no data available. ^Including insulin glargine, insulin detemir, insulin /or NPH (neutral protamine hagedorn) insulin. R: Randomised controlled trial, DB: Double blind, OL: Open label, AC: Active controlled, PC: Placebo controlled, DD: Double dummy. Met = metformin; Pio = pioglitazone; Ros = rosiglitazone; OADs = oral anti-diabetic drugs; SU = sulfonylureas; TZD = thiazolidinedione

## 3.2. Evaluation the quality of the included studies

The quality of the included studies assessment showed in Figure 1 and 2. Three studies were open-label design, which were not blind to participants and investigators[15,16,18]. One study did not provide the baseline of FPG[13]. All studies did not clarify the detailed about the allocation concealment and blinding of outcome assessment and other bias[6,13-18].
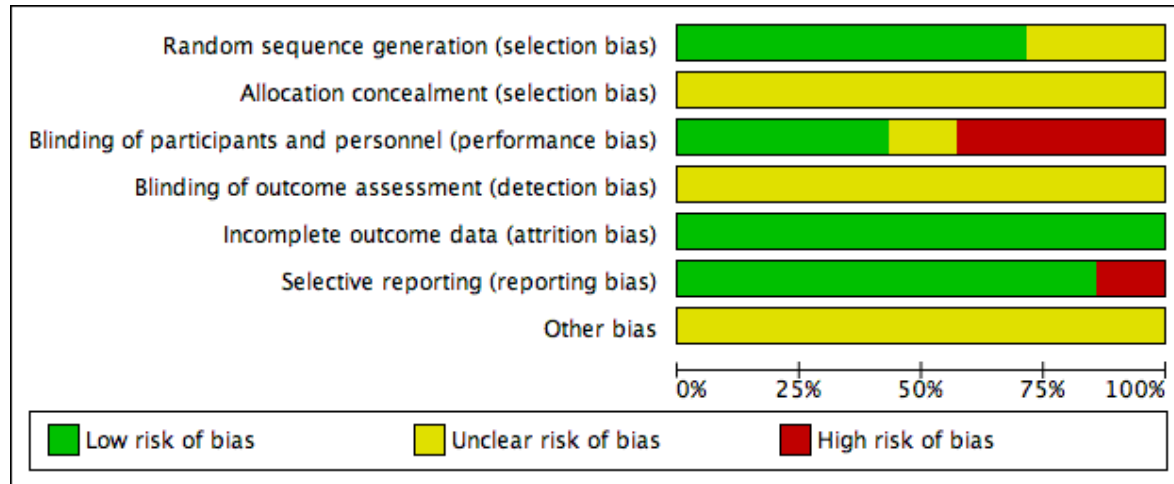


**Figure 1.** Risk of bias graph



**Figure 2.** Risk of bias summary

*Efficacy and safety of semaglutide in type 2 diabetes compared with sitagliptin,*
*exenatide ER, insulin glargine, basal insulin and placebo: a systematic review*

127

### 3.3. Efficacy outcomes: A1C, FPG, BW

The outcome of A1C and BW were available from all included studies[6,13-18], FPG were available from all studies except

SUSTAIN 6. Details are in Table 2. In SUSTAIN 6, patients were randomized to receive semaglutide (0.5 mg or 1.0 mg) or placebo.

**Table 2.** Efficacy outcomes

| Study Acronym Author, year | Mean A1C (%) Change from baseline (95% CI) | | | Mean FPG (mmol/L) Change from baseline (95% CI) | | | Mean BW (kg) Change from baseline (95% CI) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Semaglutide 1.0 mg | 0.5 mg | Placebo/ comparator | Semaglutide 1.0 mg | 0.5 mg | Placebo/ comparator | Semaglutide 1.0 mg | 0.5 mg | Placebo/ comparator |
| SUSTAIN 1 Sorli et al., 2017[13] | −1.55 (−1.74 to −1.36) | −1.45 (−1.65 to −1.26) | −0.02 (−0.23 to 0.18) | −2.34 (−2.70 to −1.98) | −2.51 (−2.87 to −2.14) | −0.55 (−0.94 to −0.16) | −4.53 (−5.34 to −3.72) | −3.73 (−4.54 to −2.91) | −0.98 (−1.82 to −0.13) |
| SUSTAIN 2 Ahrén et al., 2017[14] | −1.60 (−1.71 to −1.51) | −1.30 (−1.42 to −1.21) | −0.50 (−0.65 to −0.44) | −2.60 (−2.79 to −2.40) | −2.10 (−2.27 to −1.88) | −1.10 (−1.31 to −0.90) | −6.10 (−6.63 to −5.63) | −4.30 (−4.78 to −3.78) | −1.90 (−2.44 to −1.42) |
| SUSTAIN 3 Ahmann et al., 2016[15] | -1.50 | / | -0.90 | -2.80 | / | -2.00 | -5.60 | / | -1.90 |
| SUSTAIN 4 Aroda et al., 2017[16] | −1.64 (−1.74 to −1.54) | −1.21 (−1.31 to −1.10) | −0.83 (−0.93 to −0.73) | −2.73 (−2.96 to −2.50) | −2.04 (2.28 to −1.82) | −2.12 (−2.34 to −1.90) | −5.17 (−5.66 to −4.71) | −3.47 (−3.93 to −3.00) | 1.15 (0.70 to 1.61) |
| SUSTAIN 5 Robard et al., 2016[17] | -1.80 | -1.40 | -0.10 | -2.40 | -1.60 | -0.50 | -6.40 | -3.70 | -1.40 |
| SUSTAIN 6 Steven et al., 2016[6] | -1.40 | -1.10 | -0.40/-0.40* | NA | NA | NA | -4.90 | -3.60 | -0.50/-0.70* |
| SUSTAIN™ Seino et al., 2017[18] | -2.20 | -1.90 | -0.70 | -3.30 | -2.80 | -1.30 | -3.90 | -2.20 | 0 |

" / " = study contained only single dose of semaglutide; "NA" = no data available; * = Placebo groups contain 0.5 or 1.0 mg of placebo

### 3.4. Safety outcomes: hypoglycemia and nausea, retinopathy

The outcome of severe or blood glucose confirmed hypoglycemia were available from all included studies[6,13-18], retinopathy was available from SUSTAIN 2, 4, 6 and SUSTAIN™. Details were shown in Table 3.

**Table 3.** Safety outcomes

| Study Acronym | Author, year | Severe or BG-confirmed hypoglycemia Percentage (%) | | | Nausea Percentage (%) | | | Retinopathy Percentage (%) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Semaglutide | | Placebo/ | Semaglutide | | Placebo/ | Semaglutide | | Placebo/ |
| | | 1.0 mg | 0.5 mg | comparator | 1.0 mg | 0.5 mg | comparator | 1.0 mg | 0.5 mg | comparator |
| SUSTAIN 1 | Sorli et al., 2017[13] | 0 | 0 | 2 | 24.0 | 20.0 | 8.0 | NA | NA | NA |
| SUSTAIN 2 | Ahrén et al., 2017[14] | <1.0 | 2.0 | 1.0 | 18.0 | 18.0 | 7.0 | 0 | <1.0 | 1.0 |
| SUSTAIN 3 | Ahmann et al., 2016[15] | 7.2 | / | 2.9 | 22.0 | / | 12.0 | NA | NA | NA |
| SUSTAIN 4 | Aroda et al., 2017[16] | 6.0 | 4.0 | 11.0 | 22.0 | 21.0 | 4.0 | 0 | <1.0 | <1.0 |
| SUSTAIN 5 | Robard et al., 2016[17] | 10.7 | 8.3 | 5.3 | 16.8 | 11.4 | 4.5 | NA | NA | NA |
| SUSTAIN 6 | Steven et al., 2016[6] | 21.7 | 23.1 | 21.0/21.5* | 21.9 | 17.3 | 8.1%/7.5* | 3.0^ | | 1.8^ |
| SUSTAIN™ | Seino et al., 2017[18] | <1.0 | 0 | 0 | 12.7 | 10.7 | 0 | 2.0 | 3.8 | 3.8 |

BG = blood glucose; "NA" = no data available; * = placebo contains 0.5 and 1.0 mg groups; ^ = combined data of 0.5 and 1.0 mg from semaglutide and placebo group, respectively.

### 4. DISCUSSION AND CONCLUSIONS

Results revealed that semaglutide had more power based on A1C, FPG and BW reduction than placebo, sitagliptin, and insulin glargine. Losing weight with semaglutide intervention group, was confirmed the mechanism of GLP-1 RAs that modified the satiety and appetite in hypothalamus to reduce energy consumption to reduce body weight. In term of safety data, based on severe or BG-confirmed hypoglycemia, semaglutide has similar rate when compared to sitagliptin and exenatide ER. However, semaglutide had more nausea than others, these might be due to its action in increasing GLP-1 level compared to other comparators. Regarding specific diabetic complication such as retinopathy, the results from included studies showed that semaglutide had similar incidence of retinopathy compared to sitagliptin and insulin glargine, but more frequent when compared to placebo. However, our research still has some limitations namely

1). Our research included only RCTs of semaglutide with completed results that compared with other glucose-lowering drugs, now some other RCTs are still ongoing in clinical part, these would provide more comprehensive results. 2) The four included studies' duration was around 30 weeks, such as SUSTAIN 1, 4, 5 and TM, short duration of these studies maybe not enough to show the long-term effect of semaglutide on efficacy and safety. 3) SUSTAIN 3, 4 and TM, these studies were open-label design, once-weekly exenatide was using vial and syringe, while semaglutide was using prefilled pen injector, the frequency of dosing and titration of insulin glargine and sitagliptin was different from semaglutide. Therefore, the open-label design may bring some risk of bias, since it may sometimes influence the adherence of patients to the related interventions. 4) Two studies, SUS-TAIN 6 and TM, enrolled both male and female participants; but the ratio of male versus female was nearly 2-3 times, may

*Efficacy and safety of semaglutide in type 2 diabetes compared with sitagliptin,*
*exenatide ER, insulin glargine, basal insulin and placebo: a systematic review*

129

not correctly represent the T2DM population around the world.

In conclusion, semaglutide seems to be a new promising drug for diabetes management; however, more RCTs with well design of semaglutide versus other GLP-1 RAs that evaluate long term efficacy and safety are still needed.

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