

Semaglutide for the Treatment of Type 2 Diabetes Mellitus

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Abstract

Objective: To detail studies investigating the efficacy/safety of semaglutide as a glucagon-like peptide-1 receptor agonist (GLP-1 RA) in the treatment of type 2 diabetes mellitus. **Data Sources:** A literature search in MEDLINE and ClinicalTrials.gov (January 2013 to May 2018) using the terms *semaglutide*, *SUSTAIN*, *oral*, and *PIONEER* resulted in 10 published articles and 14 ongoing/unpublished articles. **Study Selection and Data Extraction:** All English language phase 2 and 3 clinical trials evaluating efficacy/safety of semaglutide were included. **Data Synthesis:** In 9 phase 3, multicenter SUSTAIN trials, the efficacy and safety of semaglutide have been compared with placebo and other pharmacologic therapy for diabetes (PTD). In these trials, semaglutide resulted in lower hemoglobin A_{1c} (HbA_{1c}; approximately -1.5%) and weight reductions (approximately -4.5 kg) as comparable with dulaglutide for HbA_{1c} lowering (approximately -1.5%). Semaglutide also has cardiovascular (CV) outcomes data that show significant reduction in risk of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke (hazard ratio = 0.74; 95% confidence interval = 0.58-0.95). A safety finding that emerged from the CV outcomes trial was an association of semaglutide treatment with an increased risk of retinopathy complications in patients with preexisting diabetic retinopathy. Phase 3 trial data assessing semaglutide oral formulation have shown similar HbA_{1c} (approximately -1.5% for 14 mg dose) and body weight (approximately -4.1 kg for 14 mg dose) reductions as compared with placebo. Across these studies, semaglutide was generally well tolerated with the most common adverse event reported as gastrointestinal side effects as seen in all GLP-1 RAs. **Conclusions:** These results suggest that semaglutide may have a place in therapy as a GLP-1 RA add-on therapy with higher weight loss as compared with other GLP-1 RAs and PTD and CV benefit.

Keywords

diabetes, type 2 diabetes, clinical practice, drug trials, drug safety

Introduction

The 2017 National Diabetes Statistics Report indicates that 30.3 million people in the United States have diabetes with an estimated incidence of 1.5 million cases. Of the 30.3 million people affected, 90% to 95% of these cases are type 2 diabetes mellitus (T2DM).¹ T2DM is a complex disease characterized by progressive loss of pancreatic β -cell insulin secretion and insulin resistance leading to variable blood glucose levels.²

The glucagon-like peptide-1 receptor agonist (GLP-1 RA) drug class is indicated for the treatment of T2DM. Medications in this group include the following: Trulicity (dulaglutide), Byetta (exenatide), Bydureon, Bydureon BCise (exenatide extended release [ER]), Victoza (liraglutide), and Adlyxin (lixisenatide). These are subcutaneous injectable agents that activate the GLP-1 receptors leading to increased glucose-dependent insulin secretion, decreased glucose-dependent glucagon secretion, slowed gastric emptying, and increased

satiety.² GLP-1 RAs decrease hemoglobin A_{1c} (HbA_{1c}) and provide benefits such as weight loss, low risk of hypoglycemia, and some cardiovascular (CV) protection as compared with other agents.³ With the benefits beyond glucose control capabilities, GLP-1 RAs offer more acceptable clinical application profiles for providers managing patients with T2DM. Novo Nordisk, Inc, recently developed a new GLP-1 RA, Ozempic (semaglutide), which was approved by the US Food and Drug Administration on December 5, 2017.⁴

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This article reviews clinical trials assessing semaglutide and offers clinical details to further understand its role as a glucose-lowering medication for patients with T2DM.

Data Selection

A MEDLINE search for primary literature published from January 1, 2013, to May 31, 2018, was performed using search terms *semaglutide* and *SUSTAIN* and *semaglutide* and *oral*. ClinicalTrials.gov website was also reviewed with terms *semaglutide* and *SUSTAIN* and *semaglutide* and *PIONEER*. A total of 10 published articles and 14 ongoing/unpublished articles were identified.

Pharmacology, Pharmacodynamics, and Pharmacokinetics

Semaglutide is a GLP-1 RA of human GLP-1 with 94% sequence homology. Semaglutide contains a peptide backbone with the addition of a hydrophilic spacer and C18 fatty di-acid at position 26 lysine and modifications at positions 8 and 34. These modifications result in albumin binding and protection from the enzyme dipeptidyl peptidase-4 degradation. In a glucose-dependent manner, inhibition of glucagon (fasting/postprandial) secretion, enhanced stimulation of insulin (first-/second-phase release), and slight delay in postprandial gastric emptying are responsible for the glucose lowering effects.⁵ Following a carbohydrate-rich breakfast, semaglutide has been shown to reduce 1-hour gastric emptying by 27% as compared with placebo.⁶ Concentrations of subcutaneous semaglutide peak within 3 days and steady state is achieved by week 5 of once-weekly administration. The plasma concentration of subcutaneous semaglutide exhibits dose-proportional increases with once-weekly administration; however, increased body weight has shown to decrease exposure. The elimination half-life ($t_{1/2}$) is 1 week, and the drug stays in circulation for approximately 5 weeks after the last dose.⁷ The majority of excretion is through urine and feces, with only 3% of dose unchanged in the urine. Semaglutide is more than 99% bound to plasma albumin, which contributes to the prolonged exposure.^{5,7}

Dosage Recommendations

The dosage form of semaglutide is a 2 mg/1.5 mL injection available in 2 single-use prefilled pen formulations: a pen that delivers 0.25 mg or 0.5 mg per injection and a pen that delivers 1.0 mg per injection. Semaglutide should be administered subcutaneously once weekly without regard to meals. Semaglutide should be commenced at 0.25 mg weekly subcutaneously, then increased to 0.5 mg after 4 weeks. If further glucose control is needed after 4 weeks of the 0.5 mg dose, the maximum dose of 1.0 mg may be

achieved. Semaglutide does not require dose adjustments for renal or hepatic impairment.⁵

Clinical Studies Evaluating Efficacy

The efficacy of once-weekly semaglutide 0.5 mg and 1.0 mg has been compared with placebo, oral pharmacologic therapy for diabetes (PTD), GLP-1 RAs, and basal insulin in 9 completed and 4 ongoing phase 3 multicenter studies: the SUSTAIN program.⁸⁻²⁰ SUSTAIN trials 8, 9, 10, and CHINA-MRCT are ongoing and will be excluded from further review.¹⁵⁻¹⁸ In completed studies, both doses of semaglutide significantly reduced HbA_{1c} and body weight as compared with the control treatment (Table 1).^{8-14,19,20} SUSTAIN studies 2, 3, 4, 5, and 7 showed superiority at improving glycemic control and reducing body weight as compared with sitagliptin, exenatide ER 2.0 mg, insulin glargine U100, placebo as add-on therapy to basal insulin alone or in combination with metformin, and dulaglutide, respectively.^{9-12,14} SUSTAIN 1 was a 7-month study conducted in adults with T2DM using diet and exercise. At 7 months, the HbA_{1c} and body weight were significantly lowered by 0.5 mg and 1.0 mg semaglutide as compared with diet and exercise alone. Both doses of semaglutide had similar HbA_{1c} reductions.⁸ SUSTAIN 2 used sitagliptin as a comparator and included adults with T2DM using oral PTD (metformin, pioglitazone, rosiglitazone, or combo of metformin and pioglitazone, or metformin and rosiglitazone). At 1 year, the mean HbA_{1c} and body weight were significantly reduced by both doses of semaglutide as compared with sitagliptin.⁹ SUSTAIN 3 compared semaglutide 1.0 mg with exenatide ER 2.0 mg and included patients with T2DM that were on 1 or 2 oral PTD (metformin, thiazolidinedione, and/or sulfonylurea [SFU]). Semaglutide significantly reduced both the mean HbA_{1c} and body weight after 1 year.¹⁰ In SUSTAIN 4, semaglutide or insulin glargine U100 were added on to pretrial treatment of metformin alone or in combination with a SFU in patients with T2DM. Insulin glargine U100 was initiated at 10 units once daily and titrated weekly to a fasting self-measured plasma glucose target of 72 to 99 mg/dL with an average insulin glargine dose of 29.2 units per day at the end of the study. By 7 months, both doses of semaglutide significantly reduced the mean HbA_{1c} and body weight as compared with insulin glargine U100; however, the 1.0 mg semaglutide dose resulted in greater lowering versus the 0.5 mg dose (−0.43% difference for HbA_{1c} between the 2 doses).¹¹ SUSTAIN 5 compared semaglutide versus placebo as add-on therapy to basal insulin alone or in combination with metformin in patients with T2DM. Both semaglutide doses significantly decreased mean HbA_{1c} and body weight as compared with placebo by 7 months.^{1c} Both doses lowered HbA_{1c} similarly.¹² In SUSTAIN 1, 2, 4, and 5, the 1.0 mg semaglutide dose had a greater reduction in body weight as compared with the 0.5 mg dose.^{8,9,11,12}

Table 1. Efficacy of Semaglutide Across the Phase 3 Clinical Trials.

Study	Patient Population	Duration (weeks)	Treatment	Mean Baseline HbA _{1c} and Body Weight	Change in Mean HbA _{1c} (%) From Baseline to End of Treatment	Change in Mean Body Weight (kg) From Baseline to End of Treatment
SUSTAIN 1, ⁹ NCT02054897	Age ≥ 18 yo, TZDM, treated with diet and exercise alone for ≥ 30 days before screening. HbA _{1c} = 7.0% to 10.0%	30	<ul style="list-style-type: none"> 0.5 mg SC semaglutide QW 1.0 mg SC semaglutide QW Volume-matched SC placebo QW 	<ul style="list-style-type: none"> 8.05% 91.93 kg 	<ul style="list-style-type: none"> 0.5 mg semaglutide: -1.45 ETD versus placebo (95% CI = -1.43 [-1.71 to -1.15], P < .0001) 1.0 mg semaglutide: -1.55 ETD versus placebo (95% CI = -1.53 [-1.81 to -1.25], P < .001) 	<ul style="list-style-type: none"> 0.5 mg semaglutide: -3.73 ETD versus placebo (95% CI = -2.75 [-3.92 to -1.58], P < .0001) 1.0 mg semaglutide: -4.53 ETD versus placebo (95% CI = -3.56 [-4.74 to -2.38], P < .0001)
SUSTAIN 2, ⁹ NCT01930188	Age ≥ 18 yo (or ≥ 20 yo in Japan), TZDM, HbA _{1c} = 7.0% to 10.5% for 90 days before screening; treatment with metformin (≥ 1500 mg), pioglitazone (≥ 30 mg), rosiglitazone (≥ 4 mg), or combo of metformin + pioglitazone, or metformin + rosiglitazone	56	<ul style="list-style-type: none"> 0.5 mg SC semaglutide QW + oral placebo QD 1.0 mg SC semaglutide QW + oral placebo QD 100 mg sitagliptin QD + SC volume-matched (0.5 mg and 1.0 mg) placebo QW 	<ul style="list-style-type: none"> 8.1% 89.5 kg 	<ul style="list-style-type: none"> 0.5 mg semaglutide: -1.3 ETD versus sitagliptin (95% CI = -0.77 [-0.97 to -0.62], P < .0001) 1.0 mg semaglutide: -1.6 ETD versus sitagliptin (95% CI = -1.06 [-1.21 to -0.91], P < .0001) 100 mg sitagliptin: -0.5 	<ul style="list-style-type: none"> 0.5 mg semaglutide: -4.3 ETD versus sitagliptin (95% CI = -2.35 [-3.06 to -1.63], P < .0001) 1.0 mg semaglutide: -6.1 ETD versus sitagliptin (95% CI = -4.20 [-4.91 to -3.49], P < .0001) 100 mg sitagliptin: -1.9 1.0 mg semaglutide: -5.6 2.0 mg exenatide ER: -1.9 ETD (95% CI = -3.78 [-4.58 to -2.98], P < .0001)
SUSTAIN 3, ¹⁰ NCT01885208	Age ≥ 18 yo, insulin-naïve TZDM, HbA _{1c} = 7.0% to 10.5%, treatment with 1 or 2 oral PTD (metformin ≥ 1500 mg or max tolerated dose, and/or TZD, and/or SFU [at least ½ of max dose allowed]) for ≥ 90 days before screening	56	<ul style="list-style-type: none"> 1.0 mg SC semaglutide QW 2.0 mg exenatide ER QW 	<ul style="list-style-type: none"> 8.3% 95.8 kg 	<ul style="list-style-type: none"> 1.0 mg semaglutide: -1.5 2.0 mg exenatide ER: -0.9 ETD (95% CI = -0.62 [-0.80 to -0.44], P < .0001) 	<ul style="list-style-type: none"> 1.0 mg semaglutide: -5.6 2.0 mg exenatide ER: -1.9 ETD (95% CI = -3.78 [-4.58 to -2.98], P < .0001)
SUSTAIN 4, ¹¹ NCT02128932	Age ≥ 18 yo, TZDM, HbA _{1c} = 7.0% to 10.0%, treatment with metformin alone or in combo with SFU for ≥ 90 days before screening	30	<ul style="list-style-type: none"> 0.5 mg SC semaglutide QW 1.0 mg SC semaglutide QW Insulin glargine U100 once daily initiated at 10 units and titrated to target FPG of 72 to 99 mg/dL 	<ul style="list-style-type: none"> 8.17% 93.45 kg 	<ul style="list-style-type: none"> 0.5 mg semaglutide: -1.21 ETD versus insulin glargine (95% CI = -0.38 [-0.52 to -0.24], P < .0001) 1.0 mg semaglutide: -1.64 ETD versus insulin glargine (95% CI = -0.81 [-0.96 to -0.67], P < .0001) Insulin glargine: -0.83 	<ul style="list-style-type: none"> 0.5 mg semaglutide: -3.47 ETD versus insulin glargine (95% CI = -4.62 [-5.27 to -3.96], P < .0001) 1.0 mg semaglutide: -5.17 ETD versus insulin glargine (95% CI = -6.33 [-6.99 to -5.67], P < .0001) Insulin glargine: 1.15 0.5 mg semaglutide: -3.7 ETD versus placebo (95% CI = -2.31 [-3.33 to -1.29], P < .0001) 1.0 mg semaglutide: -6.4 ETD versus placebo (95% CI = -5.06 [-6.08 to -4.04], P < .0001) Placebo: -1.4
SUSTAIN 5, ¹² NCT02305381	Age ≥ 18 yo, TZDM, HbA _{1c} = 7.0% to 10.0%, treatment with basal insulin alone or in combo with metformin	30	<ul style="list-style-type: none"> 0.5 mg SC semaglutide QW 1.0 mg SC semaglutide QW SC volume-matched (0.5 mg and 1.0 mg) placebo QW 	<ul style="list-style-type: none"> 8.4% 91.7 kg 	<ul style="list-style-type: none"> 0.5 mg semaglutide: -1.4 ETD versus placebo (95% CI = -1.35 [-1.61 to -1.10], P < .0001) 1.0 mg semaglutide: -1.8 ETD versus placebo (95% CI = -1.75 [-2.01 to -1.50], P < .0001) Placebo: -0.1 	<ul style="list-style-type: none"> 0.5 mg semaglutide: -3.6 0.5 mg placebo: -0.7 ETD versus placebo (95% CI = -2.87 [-3.47 to -2.28], P < .001) 1.0 mg semaglutide: -4.9 1.0 mg placebo: -0.5 ETD versus placebo (95% CI = -4.35 [-4.94 to -3.75], P < .001)
SUSTAIN 6, ¹³ NCT01720446	Age ≥ 50 yo, TZDM, HbA _{1c} ≥ 7%, established CV disease (previous CVD, CeVD, or PVD), chronic HF (NYHA class II or III), or CKD ≥ stage 3 or age ≥ 60 yo with ≥ 1 CV risk factor; had not been treated with an antihyperglycemic drug or had been treated with ≤ 2 oral PTD, with or without basal or premixed insulin <i>Primary endpoint: was composite of first occurrence of CV death, nonfatal MI, or nonfatal CVA</i>	104	<ul style="list-style-type: none"> 0.5 mg SC semaglutide QW 1.0 mg SC semaglutide QW Volume-matched SC placebo QW 	<ul style="list-style-type: none"> 8.7% 92.1 kg 	<ul style="list-style-type: none"> 0.5 mg semaglutide: -1.1 0.5 mg placebo: -0.4 ETD versus placebo (95% CI = -0.66 [-0.80 to -0.52], P < .001) 1.0 mg semaglutide: -1.4 1.0 mg placebo: -0.4 ETD versus placebo (95% CI = -1.05 [-1.19 to -0.91], P < .001) 	<ul style="list-style-type: none"> 0.5 mg semaglutide: -3.6 0.5 mg placebo: -0.7 ETD versus placebo (95% CI = -2.87 [-3.47 to -2.28], P < .001) 1.0 mg semaglutide: -4.9 1.0 mg placebo: -0.5 ETD versus placebo (95% CI = -4.35 [-4.94 to -3.75], P < .001)

(continued)

Table 1. (continued)

Study	Patient Population	Duration (weeks)	Treatment	Mean Baseline HbA _{1c} and Body Weight	Change in Mean HbA _{1c} (%) From Baseline to End of Treatment	Change in Mean Body Weight (kg) From Baseline to End of Treatment
SUSTAIN 7, ¹⁴ NCT02648204	Age ≥ 18 yo, T2DM, HbA _{1c} = 7.0% to 10.5%, treatment with metformin (minimum of 1500 mg/day or max tolerated dose) for 90 days prior to screening	40	<ul style="list-style-type: none"> 0.5 mg SC semaglutide QW 1.0 mg SC semaglutide QW 0.75 mg dulaglutide QW 1.5 mg dulaglutide QW 	<ul style="list-style-type: none"> 8.2% 95.2 kg 	<ul style="list-style-type: none"> 0.5 mg semaglutide: -1.5 0.75 mg dulaglutide: -1.1 ETD (95% CI = -0.40 [-0.55 to -0.25], P < .0001) 1.0 mg semaglutide: -1.8 1.5 mg dulaglutide: -1.4 ETD (95% CI = -0.41 [-0.57 to -0.25], P < .001) 	<ul style="list-style-type: none"> 0.5 mg semaglutide: -4.6 0.75 mg dulaglutide: -2.3 ETD (95% CI = -2.26 [-3.02 to -1.51], P < .0001) 1.0 mg semaglutide: -6.5 1.5 mg dulaglutide: -3.0 ETD (95% CI = -3.55 [-4.32 to -2.78], P < .0001)
SUSTAIN JP PTD, ¹⁹ NCT02207374	Age ≥ 20 yo, Japanese, T2DM, HbA _{1c} = 7.0% to 10.5%, treatment with either diet and exercise for at least 30 days before visit 1 (week 2) or on oral PTD monotherapy (either of SFU, glinide, α-GI, or TZD) in addition to diet and exercise for at least 60 days before visit 1 (week 2) Primary outcome was number of AE	56	<ul style="list-style-type: none"> 0.5 mg SC semaglutide QW 1.0 mg SC semaglutide QW 1 additional oral PTD (DPP-4 inhibitor; SFU, glinide, biguanide, α-GI, or TZD) + prerinial oral PTD monotherapy, if any 	<ul style="list-style-type: none"> 8.1% 71.5 kg 	<ul style="list-style-type: none"> 0.5 mg semaglutide: -1.7 ETD versus additional oral PTD (95% CI = -1.08 [-1.24 to -0.91], P < .0001) 1.0 mg semaglutide: -2.0 ETD versus additional oral PTD (95% CI = -1.37 [-1.53 to -1.20], P < .0001) Additional oral PTD: -0.7 0.5 mg semaglutide: -1.9 ETD versus sitagliptin (95% CI = -1.13 [-1.32 to -0.94], P < .0001) 1.0 mg semaglutide: -2.2 ETD versus sitagliptin (95% CI = -1.44 [-1.63 to -1.24], P < .0001) 100 mg sitagliptin: -0.7 3 mg semaglutide: -0.8 7 mg semaglutide: -1.3 14 mg semaglutide: -1.5 Placebo: -0.1 14 mg semaglutide: -1.4[†]; -1.3 25 mg empagliflozin: -0.9[‡]; -0.8 *HbA_{1c} at 26 weeks 	<ul style="list-style-type: none"> 0.5 mg semaglutide: -1.4 ETD versus additional oral PTD (95% CI = -1.84 [-2.67 to -1.01], P < .001) 1.0 mg semaglutide: -3.2 ETD versus additional oral PTD (95% CI = -3.59 [-4.43 to -2.75], P < .001) Additional oral PTD: 0.4 0.5 mg semaglutide: -2.2 ETD versus sitagliptin (95% CI = -3.02 to -1.42], P < .0001) 1.0 mg semaglutide: -3.9 ETD versus sitagliptin (95% CI = -4.70 to -3.07], P < .0001) 100 mg sitagliptin: 0.0 3 mg semaglutide: -1.7 7 mg semaglutide: -2.5 14 mg semaglutide: -4.1 Placebo: -1.5 14 mg semaglutide: -4.2[‡]; -4.7 25 mg empagliflozin: -3.8[‡]; -3.8 *Weight loss at 26 weeks
SUSTAIN JP Mono, ²⁰ NCT02254291	Age ≥ 20 yo, T2DM, Japanese, HbA _{1c} = 6.5% to 9.5% if treated with either diet and exercise therapy + oral PTD monotherapy or HbA _{1c} = 7.0% to 10.5% if treated with diet and exercise therapy only for ≥ 30 days before screening Primary outcome was number of AE	30	<ul style="list-style-type: none"> 0.5 mg SC semaglutide QW 1.0 mg SC semaglutide QW 100 mg sitagliptin QD 	<ul style="list-style-type: none"> 8.1% 69.3 kg 	<ul style="list-style-type: none"> 0.5 mg semaglutide: -1.9 ETD versus sitagliptin (95% CI = -1.13 [-1.32 to -0.94], P < .0001) 1.0 mg semaglutide: -2.2 ETD versus sitagliptin (95% CI = -1.44 [-1.63 to -1.24], P < .0001) 100 mg sitagliptin: -0.7 3 mg semaglutide: -0.8 7 mg semaglutide: -1.3 14 mg oral semaglutide QD Oral placebo QD 14 mg oral semaglutide QD 25 mg empagliflozin QD 1500 mg or max tolerated dose) ≥ 90 days before screening 	<ul style="list-style-type: none"> 0.5 mg semaglutide: -2.2 ETD versus sitagliptin (95% CI = -3.02 to -1.42], P < .0001) 1.0 mg semaglutide: -3.9 ETD versus sitagliptin (95% CI = -4.70 to -3.07], P < .0001) 100 mg sitagliptin: 0.0 3 mg semaglutide: -1.7 7 mg semaglutide: -2.5 14 mg semaglutide: -4.1 Placebo: -1.5 14 mg semaglutide: -4.2[‡]; -4.7 25 mg empagliflozin: -3.8[‡]; -3.8 *Weight loss at 26 weeks
PIONEER 1, ^{25,26} NCT02906930	Age ≥ 18 yo (or ≥ 20 yo for Japan or ≥ 19 yo for Algeria), T2DM, HbA _{1c} = 7.0% to 9.5%, treatment with diet and exercise for ≥ 30 days before screening	26	<ul style="list-style-type: none"> 3 mg oral semaglutide QD 7 mg oral semaglutide QD 14 mg oral semaglutide QD Oral placebo QD 	<ul style="list-style-type: none"> 8.0% 88 kg 	<ul style="list-style-type: none"> 3 mg semaglutide: -0.8 7 mg semaglutide: -1.3 14 mg semaglutide: -1.5 Placebo: -0.1 	<ul style="list-style-type: none"> 3 mg semaglutide: -1.7 7 mg semaglutide: -2.5 14 mg semaglutide: -4.1 Placebo: -1.5
PIONEER 2, ^{27,28} NCT02863328	Age ≥ 18 yo, T2DM, HbA _{1c} = 7.0% to 10.5%, treatment with metformin (at least 1500 mg or max tolerated dose) ≥ 90 days before screening	52	<ul style="list-style-type: none"> 14 mg oral semaglutide QD 25 mg empagliflozin QD 	<ul style="list-style-type: none"> N/A N/A 	<ul style="list-style-type: none"> 14 mg semaglutide: -1.4[†]; -1.3 25 mg empagliflozin: -0.9[‡]; -0.8 *HbA_{1c} at 26 weeks 	<ul style="list-style-type: none"> 14 mg semaglutide: -4.2[‡]; -4.7 25 mg empagliflozin: -3.8[‡]; -3.8 *Weight loss at 26 weeks

Abbreviations: α-GI, alpha-glucosidase inhibitor; AE, adverse events; CeVD, cerebrovascular disease; CV, confidence interval; CKD, chronic kidney disease; CVA, cerebrovascular attack (stroke); CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; ER, extended release; ETD, estimated treatment difference; FPG, fasting plasma glucose; glinide, meglitinides; HbA_{1c}, hemoglobin A_{1c}; HF, heart failure; MI, myocardial infarction; N/A, not available; NYHA, New York Heart Association; PTD, pharmacologic therapy for diabetes; PVD, peripheral vascular disease; QD, once daily; QW, once weekly; SC, subcutaneous; SFU, sulfonylurea; SGLT-2, sodium-glucose cotransporter-2; TZD, thiazolidinedione; yo, years old.

Table 2. Cardiovascular Outcomes Trial: SUSTAIN 6—Noninferiority Design (Superiority Margins Were Not Predefined).

Average Baseline Characteristics	Treatment	Duration	Primary Composite Endpoint: First Occurrence (n [%]) of Death From CV Causes, Nonfatal MI (Including Silent), or Nonfatal Stroke From Baseline to Week 104	Secondary Composite Endpoint: First Occurrence (n [%]) of an Expanded Composite CV Outcome (Death From CV Causes, Nonfatal MI, Nonfatal Stroke, Revascularization [Coronary or Peripheral], and Hospitalization for Unstable Angina or Heart Failure) From Baseline to Week 104
<ul style="list-style-type: none"> Established CVD, CKD \geqstage 3, or both: 83.0% Established CVD without CKD: 58.8% CKD only: 10.7% Ischemic heart disease: 60.5% MI: 32.5% HF: 23.6% Ischemic stroke: 11.6% Hemorrhagic stroke: 3.3% Hypertension: 92.8% 	<ul style="list-style-type: none"> 0.5 mg semaglutide QW 1.0 mg semaglutide QW SC volume-matched (0.5 mg and 1.0 mg) placebo QW 	104 weeks	<ul style="list-style-type: none"> Semaglutide: 108 (6.6%) Placebo: 146 (8.9%) Hazard ratio (95% CI = 0.74 [0.58 to 0.95], $P < .001$ noninferiority; $P = .02$ superiority) 	<ul style="list-style-type: none"> Semaglutide: 199 (12.1%) Placebo: 264 (16.0%) Hazard ratio (95% CI = 0.74 [0.62 to 0.89], $P = .002$)

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; HF, heart failure; MI, myocardial infarction; QW, once weekly; SC, subcutaneous.

SUSTAIN 6 evaluated CV outcomes for both doses of semaglutide versus placebo and included adults with T2DM and high CV risk with no PTD or ≤ 2 oral PTD with or without insulin (Table 2). High CV risk was defined by 2 categories in the study. The first category was defined as age 50 years and older with established CV disease including at least one of the following: prior myocardial infarction; stroke or transient ischemic attack; arterial revascularization; more than 50% stenosis of coronary, carotid, or lower extremities arteries; symptomatic coronary heart disease; asymptomatic cardiac ischemia; New York Heart Association class II to III chronic heart failure; and chronic renal impairment with an estimated glomerular filtration rate < 60 mL/min/1.73 m². The second category was defined as age 60 years and older with at least one of the following CV risk factors: microalbuminuria (30–299 mg/g or proteinuria); hypertension with left ventricular hypertrophy; left ventricular systolic or diastolic dysfunction; and ankle/brachial index < 0.9 . As for glycemic efficacy, both doses significantly lowered mean HbA_{1c} and body weight as compared with placebo after 2 years; however, the 1.0 mg semaglutide dose lowered body weight further as compared with the 0.5 mg dose (−1.3 kg difference). As for lowering CV risk, patients receiving semaglutide had a significant 26% lower risk of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke as compared with patients taking placebo after 2 years. The study does not report the differences in outcomes of the 2 doses of semaglutide and rather analyzes both doses together.¹³

SUSTAIN 7 evaluated semaglutide versus dulaglutide and included patients with T2DM and pretrial treatment of metformin. Both doses of semaglutide resulted in greater reductions of HbA_{1c} and body weight as compared with both doses of dulaglutide over 9 months. Semaglutide 0.5 mg had similar HbA_{1c} reductions, but greater reduction of body weight as compared with dulaglutide 1.5 mg.¹⁴

Two additional Japanese SUSTAIN trials, JP PTD and JP Mono, included Japanese patients with T2DM and pretrial treatment of diet and exercise alone and/or oral PTD (or oral antidiabetic drug as used in the study) monotherapy. The JP PTD trial used add-on oral PTD (dipeptidyl peptidase-4 inhibitor, biguanide, SFU, glinide, α -glucosidase inhibitor, or thiazolidinedione) as a comparator and JP Mono used sitagliptin. Both trials showed significantly greater reductions in mean HbA_{1c} and body weight for both doses of semaglutide as compared with add-on therapy over 1 year (JP PTD) or sitagliptin over 7 months (JP Mono).^{19,20}

Clinical Trials Evaluating Safety

Across the SUSTAIN studies, similar adverse events were reported for semaglutide with the most common as mild to moderate gastrointestinal adverse events seen throughout the GLP-1 RA class.⁸ In particular, nausea is typically present at initiation of semaglutide and diminishes over time.

Semaglutide had a $< 3\%$ rate of severe or blood glucose confirmed symptomatic hypoglycemic episodes in SUSTAIN studies 1, 2, 7, JP PTD, and JP Mono (Table 3).^{8,9,14,19,20}

Table 3. Safety of Semaglutide Across the Phase 3 Clinical Trials.

Study	# of Severe or Blood Glucose-Confirmed Symptomatic Hypoglycemic Episodes During Exposure of Drug	Pancreatitis, n (%)	Cholelithiasis, n (%)	Malignant Neoplasms, n (%)	Retinopathy Complications*, n (%)	New or Worsening Nephropathy, n (%)
SUSTAIN 1, ⁸ NCT02054897	<ul style="list-style-type: none"> For all treatment arms: 0 	<ul style="list-style-type: none"> For all treatment arms: 0 	<ul style="list-style-type: none"> 0.5 mg semaglutide: 3 (2%) 1.0 mg semaglutide: 1 (<1%) Placebo: 0 	<ul style="list-style-type: none"> 0.5 mg semaglutide: 2 (2%) 1.0 mg semaglutide: 2 (2%) Placebo: 0 	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> N/A
SUSTAIN 2, ⁹ NCT01930188	<ul style="list-style-type: none"> 0.5 mg semaglutide: 7 (2%) 1.0 mg semaglutide: 2 (<1%) 100 mg sitagliptin: 5 (1%) <p>No severe hypoglycemic events were noted in semaglutide groups</p>	<ul style="list-style-type: none"> 0.5 mg semaglutide: acute = 3 (1%); chronic = 0 1.0 mg semaglutide: acute = 0; chronic = 1 (<1%) 100 mg sitagliptin: 0 	<ul style="list-style-type: none"> 0.5 mg semaglutide: 1 (<1%) 1.0 mg semaglutide: 7 (2%) 100 mg sitagliptin: 6 (1%) 	<ul style="list-style-type: none"> 0.5 mg semaglutide: 0 1.0 mg semaglutide: 2 (<1%) 100 mg sitagliptin: 2 (<1%) 	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> N/A
SUSTAIN 3, ¹⁰ NCT01885208	<ul style="list-style-type: none"> 1.0 mg semaglutide: 33 (8.2%) 2.0 mg exenatide ER: 33 (8.1%) 	<ul style="list-style-type: none"> 1.0 mg semaglutide: 2 (0.5%) 2.0 mg exenatide ER: 3 (0.7%) 	<ul style="list-style-type: none"> 1.0 mg semaglutide: 6 (1.5%) 2.0 mg exenatide ER: 2 (0.5%) 	<ul style="list-style-type: none"> 1.0 mg semaglutide: 8 (2%) 2.0 mg exenatide ER: 2 (0.5%) 	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> N/A
SUSTAIN 4, ¹¹ NCT02128932	<ul style="list-style-type: none"> 0.5 mg semaglutide: 16 (4%) 1.0 mg semaglutide: 20 (6%) Insulin glargine: 38 (11%) 	<ul style="list-style-type: none"> 0.5 mg semaglutide: 2 (1%) 1.0 mg semaglutide: 0 Insulin glargine: 0 	<ul style="list-style-type: none"> 0.5 mg semaglutide: 2 (1%) 1.0 mg semaglutide: 2 (1%) Insulin glargine: 1 (<1%) 	<ul style="list-style-type: none"> 0.5 mg semaglutide: 0 1.0 mg semaglutide: 0 Insulin glargine: 1 (<1%) 	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> N/A
SUSTAIN 5, ¹² NCT02305381	<ul style="list-style-type: none"> 0.5 mg semaglutide: 11 (8.3%) 1.0 mg semaglutide: 14 (10.7%) Placebo: 7 (5.3%) 	<ul style="list-style-type: none"> All treatment arms: 0 	<ul style="list-style-type: none"> 0.5 mg semaglutide: 3 (2.3%) 1.0 mg semaglutide: 1 (0.8%) Placebo: 0 	<ul style="list-style-type: none"> 0.5 mg semaglutide: 1 (0.8%) 1.0 mg semaglutide: 1 (0.8%) Placebo: 0 	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> N/A
SUSTAIN 6, ¹³ NCT01720446	<ul style="list-style-type: none"> 0.5 mg semaglutide: 191 (23.1%) 1.0 mg semaglutide: 178 (21.7%) 0.5 mg placebo: 177 (21.5%) 1.0 mg placebo: 173 (21.0%) 	<ul style="list-style-type: none"> 0.5 mg semaglutide: 6 (0.7%) 1.0 mg semaglutide: 3 (0.4%) 0.5 mg placebo: 3 (0.4%) 1.0 mg placebo: 9 (1.1%) 	<ul style="list-style-type: none"> 0.5 mg semaglutide: 21 (2.5%) 1.0 mg semaglutide: 17 (2.1%) 0.5 mg placebo: 19 (2.3%) 1.0 mg placebo: 12 (1.5%) 	<ul style="list-style-type: none"> 0.5 mg semaglutide: 26 (3.1%) 1.0 mg semaglutide: 40 (4.9%) 0.5 mg placebo: 35 (4.2%) 1.0 mg placebo: 35 (4.2%) 	<ul style="list-style-type: none"> Semaglutide: 50 (3.0%) Placebo: 29 (1.8%) Hazard ratio (95% CI) = 1.76 [1.1 to 2.78], P = .02 	<ul style="list-style-type: none"> Semaglutide: 62 (3.8%) Placebo: 100 (6.1%) Hazard ratio (95% CI) = 0.64 [0.46 to 0.88], P = .005
SUSTAIN 7, ¹⁴ NCT02648204	<ul style="list-style-type: none"> 0.5 mg semaglutide: 2 (1%) 0.75 mg dulaglutide: 3 (1%) 1.0 mg semaglutide: 5 (2%) 1.5 mg dulaglutide: 5 (2%) 	<ul style="list-style-type: none"> 0.5 mg semaglutide: 0 0.75 mg dulaglutide: 0 1.0 mg semaglutide: 0 1.5 mg dulaglutide: 0 	<ul style="list-style-type: none"> 0.5 mg semaglutide: 0 0.75 mg dulaglutide: 1 (<1%) 1.0 mg semaglutide: 2 (1%) 1.5 mg dulaglutide: 2 (1%) 	<ul style="list-style-type: none"> 0.5 mg semaglutide: 3 (1%) 0.75 mg dulaglutide: 1 (<1%) 1.0 mg semaglutide: 3 (1%) 1.5 mg dulaglutide: 3 (1%) 	<ul style="list-style-type: none"> 0.5 mg semaglutide: 2 (1%) 0.75 mg dulaglutide: 2 (1%) 1.0 mg semaglutide: 2 (1%) 1.5 mg dulaglutide: 3 (1%) 	<ul style="list-style-type: none"> N/A
SUSTAIN JP PTD, ¹⁹ NCT02207374	<ul style="list-style-type: none"> 0.5 mg semaglutide: 3 (1.3%) 1.0 mg semaglutide: 6 (2.5%) Additional PTD: 1.7 (2%) 	<ul style="list-style-type: none"> All treatment arms: 0 	<ul style="list-style-type: none"> 0.5 mg semaglutide: 4 (1.7%) 1.0 mg semaglutide: 2 (0.8%) Additional PTD: 0 	<ul style="list-style-type: none"> 0.5 mg semaglutide: 4 (1.7%) 1.0 mg semaglutide: 3 (1.2%) Additional PTD: 3 (2.5%) 	<ul style="list-style-type: none"> 0.5 mg semaglutide: 4 (1.7%) 1.0 mg semaglutide: 1 (1%) Additional PTD: 6 (5.0%) 	<ul style="list-style-type: none"> N/A
SUSTAIN JP Mono, ²⁰ NCT02254291	<ul style="list-style-type: none"> 0.5 mg semaglutide: 0 1.0 mg semaglutide: 1 (1%) 100 mg sitagliptin: 0 N/A 	<ul style="list-style-type: none"> All treatment arms: 0 	<ul style="list-style-type: none"> 0.5 mg semaglutide: 0 1.0 mg semaglutide: 1 (1%) 100 mg sitagliptin: 0 N/A 	<ul style="list-style-type: none"> 0.5 mg semaglutide: 0 1.0 mg semaglutide: 1 (1%) 100 mg sitagliptin: 1 (1%) N/A 	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> N/A
PIONEER 1, ^{25,26} NCT02906930	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> N/A
PIONEER 2, ^{27,28} NCT02863328	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> N/A

Abbreviations: CI, confidence interval; ER, extended release; N/A, not available; PTD, pharmacologic therapy for diabetes.

*Vitreous hemorrhage, onset of diabetes-related blindness, and need for treatment with an intravitreal agent or retinal photocoagulation.

SUSTAIN trials 3, 4, 5, and 6 had higher rates of hypoglycemic episodes for semaglutide with SUSTAIN 6 having the highest rate of 23.1% for 0.5 mg semaglutide.¹⁰⁻¹³ In these trials, insulin or insulin secretagogues were used as comparator or background treatments.

The occurrence of acute pancreatitis events was low and reported as $\leq 1\%$ throughout the SUSTAIN trials for both doses of semaglutide. The comparator groups in these studies (placebo, sitagliptin, exenatide ER, insulin glargine, dulaglutide) exhibited comparable occurrences of acute pancreatitis events with the highest occurrence of 1.1% for placebo in the SUSTAIN 6 trial.^{8-14,19,20} Most of the pancreatitis episodes were classified as mild. The rate of cholelithiasis was $\leq 2.5\%$, and the incidence of malignant neoplasms was $\leq 4.9\%$ across the SUSTAIN trials for semaglutide.^{8-14,19,20} More malignant neoplasms were reported in the semaglutide groups in SUSTAIN trials 1, 3, 4 (0.5 mg dose only), 5, and 6 (1.0 mg dose only).^{8,10-13} In SUSTAIN 3, malignant neoplasms occurred at a higher frequency in the semaglutide group versus exenatide ER (2% vs 0.5%) with no pattern of organ distribution.¹⁰ Although SUSTAIN 6 reported a higher rate of malignant neoplasms in the 1.0 mg semaglutide group, the rates were similar among the semaglutide and placebo groups.¹³ The incidence of thyroid malignant neoplasms was low in the SUSTAIN trials. SUSTAIN 2 reported 1 case of papillary thyroid cancer in the 1.0 mg semaglutide group.⁹ SUSTAIN 6 did not report any medullary thyroid carcinomas in the trial.¹³ SUSTAIN JP Mono did not show any thyroid neoplasms or medullary thyroid carcinomas, and SUSTAIN JP PTD did not report medullary thyroid carcinomas either.^{19,20}

As for immunogenicity, SUSTAIN studies 1, 2, 3, 6, JP Mono, and JP PTD had subjects that developed antibodies against semaglutide.^{8-10,13,19,20} However, most of the anti-semaglutide antibodies did not neutralize semaglutide or endogenous GLP-1 *in vitro*. SUSTAIN 6 had only 4 patients with antibodies during follow-up (30 patients initially) and only 1 subject in SUSTAIN JP Mono had anti-semaglutide antibodies throughout the trial that resulted in a negative antibody test at follow-up.^{13,20} The decrease in number of subjects with a positive antibody test at follow-up suggests that the antibody formation is transient.

SUSTAIN 6 trial found that subjects receiving semaglutide had a significant 36% lower risk of new or worsening nephropathy, but a significant 76% higher risk of retinopathy complications (vitreous hemorrhage, blindness, or circumstances requiring treatment with an intravitreal agent or photocoagulation) as compared with placebo. Although the occurrence of retinopathy complications was low in the semaglutide pooled groups (3%), 66 out of the 79 patients (83.5%) with retinopathy complications had baseline retinopathy (42 out of 50 semaglutide group patients [84.0%] and 24 out of 29 placebo group patients [82.8%]).¹³ Retinopathy complications are unique to semaglutide

within the GLP-1 RA class and may require additional monitoring. A possible theory for the increased retinopathy complications is the relationship between worsening retinopathy and rapid glucose reductions that have been previously described in insulin-dependent patients.^{21,22} However, this proposed association does not eliminate the possibility of semaglutide having a direct effect on patients' eyes.¹³

Place in Therapy

According to the 2018 American Diabetes Association (ADA) Standards of Medical Care in Type 2 Diabetes Mellitus, GLP-1 RAs are recommended as an option for dual therapy if metformin monotherapy is not effective in achieving the HbA_{1c} target within 3 months of treatment. The 2018 ADA guidelines recommend adding an agent with CV risk reduction data for patients with atherosclerotic CV disease (ASCVD). Of the GLP-1 RAs, liraglutide in the LEADER trial was shown to reduce CV events in patients with high CV risk and is recommended in ASCVD patients in the 2018 ADA guidelines.^{2,23} SUSTAIN 6 trial for semaglutide included similar high CV risk patients as the LEADER trial and the CV risk reduction was consistent with liraglutide.^{13,23} The evidence suggests that semaglutide may be an option to lower CV risk in patients with T2DM and ASCVD.

Semaglutide may have a benefit over other GLP-1 RAs with regard to greater weight reduction, use in renal impairment, and potential oral tablet formulation. Semaglutide provides greater weight loss reduction of roughly 4 kg while the other GLP-1 RAs reduce body weight by approximately 1.4 to 2.5 kg. In addition, semaglutide does not require renal dose adjustments unlike exenatide and exenatide ER.²⁴ Semaglutide also has an oral tablet formulation in phase 3 clinical trials (the PIONEER program), which is unique within the GLP-1 RA class of subcutaneous injections. The phase 3 trial, PIONEER 1, assessed the efficacy and safety of once-daily oral semaglutide in 3, 7, and 14 mg doses as compared with placebo in patients with T2DM using diet and exercise alone. Patients treated with oral semaglutide exhibited greater HbA_{1c} reductions as compared with placebo (3 mg dose lowered HbA_{1c} by 0.8%; 7 mg dose resulted in 1.3% HbA_{1c} reduction; and 14 mg dose reduced HbA_{1c} by 1.5% vs 0.1% HbA_{1c} reduction in placebo group patients). As for weight loss, the 3 mg oral semaglutide reduced body weight by 1.7 kg; the 7 mg dose lowered body weight by 2.5 kg; and the 14 mg dose reduced body weight by 4.1 kg as compared with a weight loss of 1.5 kg in the placebo group patients.^{25,26} PIONEER 2 assessed efficacy and safety of 14 mg oral semaglutide as compared with 25 mg empagliflozin in patients with T2DM treated with metformin. Patients treated with 14 mg oral semaglutide demonstrated statistically significant reductions in HbA_{1c} and body weight as compared with empagliflozin over 52

weeks.^{27,28} A phase 2 study comparing different oral dosages of semaglutide tablets with subcutaneous semaglutide showed that the 40 mg tablet lowered HbA1c and body weight similarly to 1.0 mg subcutaneous semaglutide; however, the 40 mg tablet at standard dose escalation resulted in more gastrointestinal adverse events.²⁹

Summary

Semaglutide is a recently approved GLP-1 RA with a long duration of action allowing for once-weekly dosing. Semaglutide is administered subcutaneously, but may eventually be available as an oral tablet formulation. The SUSTAIN trial program has shown that semaglutide improves glycemic control and provides weight loss in patients with T2DM, with evidence for CV risk reduction and higher risk of retinopathy complications. More data need to be evaluated to find out the causality of retinopathy noted. However, a risk versus benefit discussion with patients is essential.

Declaration of Conflicting Interests

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References

- Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2017: estimates of diabetes and its burden in the United States. <https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf>. Accessed July 17,2018.
- American Diabetes Association. Standards of medical care in diabetes—2018. *Diabetes Care*. 2018;41(suppl 1):S1-S159. http://care.diabetesjournals.org/content/diacare/suppl/2017/12/08/41_Supplement_1.DC1/DC_41_S1_Combined.pdf. Published January 2018. Accessed July 17,2018.
- Prasad-Reddy L, Isaacs D. A clinical review of GLP-1 receptor agonists: efficacy and safety in diabetes and beyond. *Drugs Context*. 2015;4:212283. doi:10.7573/dic.212283.
- US Food and Drug Administration. Drug Trial Snapshot: Ozempic. <https://www.fda.gov/Drugs/InformationOnDrugs/ucm590624.htm>. Accessed July 17,2018.
- Ozempic [package insert]. Plainsboro, NJ: Novo Nordisk Inc; 2017.
- Hjerpsted JB, Flint A, Brooks A, Axelsen MB, Kvist T, Blundell J. Semaglutide improves postprandial glucose and lipid metabolism, and delays first-hour gastric emptying in subjects with obesity. *Diabetes Obes Metab*. 2018;20:610-619. doi:10.1111/dom.13120.
- Truven Health Analytics. IBM Micromedex Web Application Access. *Semaglutide*. <http://www.micromedexsolutions.com>. Accessed July 17,2018.
- Sorli C, Harashima S, Tsoukas GM, et al. Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. *Lancet Diabetes Endocrinol*. 2017;5:251-260. doi:10.1016/S2213-8587(17)30013-X.
- Ahrén B, Masmiquel L, Kumar H, et al. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. *Lancet Diabetes Endocrinol*. 2017;5:341-354. doi:10.1016/S2213-8587(17)30092-X.
- Ahmann AJ, Capehorn M, Charpentier G, et al. Efficacy and safety of semaglutide once-weekly semaglutide versus exenatide ER in subjects with type 2 diabetes (SUSTAIN 3): a 56-week, open-label, randomized clinical trial. *Diabetes Care*. 2018;41:258-266. doi:10.2337/dc17-0417.
- Aroda VR, Bain SC, Cariou B, et al. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naïve patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. *Lancet Diabetes Endocrinol*. 2017;5:355-366. doi:10.1016/S2213-8587(17)30085-2.
- Rodbard HW, Lingvay I, Reed J, et al. 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™ 5). Poster presented at: European Association for the Study of Diabetes Annual Meeting; September 12-16, 2016; Munich, Germany.
- Marso SP, Bain SC, Consoli A, et al; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375:1834-1844. doi:10.1056/NEJMoA1607141.
- Pratley RE, Aroda VR, Lingvay I, et al; SUSTAIN 7 Investigators. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. *Lancet Diabetes Endocrinol*. 2018;6:275-286. doi:10.1016/S2213-8587(18)30024-X.
- US National Library of Medicine. ClinicalTrials.gov. Efficacy and safety of semaglutide versus canagliflozin as add-on to metformin in subjects with type 2 diabetes (SUSTAIN 8). <https://clinicaltrials.gov/ct2/show/NCT03136484>. Published May 2, 2017. Accessed July 17,2018.
- US National Library of Medicine. ClinicalTrials.gov. Efficacy and safety of semaglutide once-weekly versus placebo as add-on to SGLT-2i in subjects with type 2 diabetes mellitus (SUSTAIN 9). <https://clinicaltrials.gov/ct2/show/NCT03086330> Published March 22, 2017. Accessed July 17,2018.
- US National Library of Medicine. ClinicalTrials.gov. Research study comparing a new medicine semaglutide to liraglutide

- in people with type 2 diabetes (SUSTAIN 10). <https://www.clinicaltrials.gov/ct2/show/study/NCT03191396>. Published June 19, 2017. Accessed July 17,2018.
18. US National Library of Medicine. ClinicalTrials.gov. Efficacy and safety of semaglutide once-weekly versus sitagliptin once-daily as add-on to metformin in subjects with type 2 diabetes (SUSTAIN-CHINA MRCT) (SUSTAIN). <https://clinicaltrials.gov/ct2/show/NCT03061214>. Published February 23, 2017. Accessed July 17,2018.
 19. Kaku K, Yamada Y, Watada H, et al. Safety and efficacy of once-weekly semaglutide vs additional oral antidiabetic drugs in Japanese people with inadequately controlled type 2 diabetes: a randomized trial. *Diabetes Obes Metab*. 2018;20:1202-1212. doi:10.1111/dom.13218.
 20. Seino Y, Terauchi Y, Osonoi T, et al. Safety and efficacy of semaglutide once weekly vs sitagliptin once daily, both as monotherapy in Japanese people with type 2 diabetes. *Diabetes Obes Metab*. 2018;20:378-388. doi:10.1111/dom.13082.
 21. Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. *Arch Ophthalmol*. 1998;116:874-886. doi:10.1001/archophth.116.7.874.
 22. Dahl-Jorgensen K, Brinchmann-Hansen O, Hanssen KF, Sandvik L, Aagenaes O. Rapid tightening of blood glucose control leads to transient deterioration of retinopathy in insulin dependent diabetes mellitus: the Oslo study. *Br Med J (Clin Res Ed)*. 1985;290:811-815.
 23. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375:311-322. doi:10.1056/NEJMoa1603827.
 24. Pharmacist's Letter. Comparison of GLP-1 agonists. <https://pharmacist.therapeuticresearch.com/Content/Segments/PRL/2017/Jan/Comparison-of-GLP-1-Agonists-10594>. Accessed July 17,2018.
 25. US National Library of Medicine. ClinicalTrials.gov. Efficacy and safety of oral semaglutide versus placebo in subjects with type 2 diabetes mellitus treated with diet and exercise only (PIONEER 1). <https://clinicaltrials.gov/ct2/show/NCT02906930>. Published September 20, 2016. Accessed July 17,2018.
 26. Novo Nordisk A/S. Novo Nordisk successfully completes the first phase 3 trial, PIONEER 1, with oral semaglutide. *Global News Wire*. <https://globenewswire.com/news-release/2018/02/22/1379640/0/en/Novo-Nordisk-successfully-completes-the-first-phase-3a-trial-PIONEER-1-with-oral-semaglutide.html>. Published February 22, 2018. Accessed July 17,2018.
 27. US National Library of Medicine. ClinicalTrials.gov. Efficacy and safety of oral semaglutide versus empagliflozin in subjects with type 2 diabetes mellitus (PIONEER 2). <https://clinicaltrials.gov/ct2/show/NCT02863328?term=PIONEER%2C+semaglutide&rank=4>. Published August 11, 2016. Accessed July 17, 2018.
 28. Novo Nordisk A/S. Oral semaglutide shows superior improvement in HbA1c vs empagliflozin in the PIONEER 2 Trial. <https://www.novonordisk.com/media/news-details.2195846.html>. Published May 29, 2018. Accessed July 17,2018.
 29. Davies M, Pieber TR, Hartoft-Nielsen M, Hansen OKH, Jabbour S, Rosenstock J. Effect of oral semaglutide compared with placebo and subcutaneous semaglutide on glycemic control in patients with type 2 diabetes: a randomized clinical trial. *JAMA*. 2017;318:1460-1470. doi:10.1001/jama.2017.1475.