PharmaNote

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Semaglutide (Ozempic®): A New GLP-1 Agonist for Type 2 Diabetes Mellitus

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Diabetes was the 7th leading cause of death in 2015 according to the Centers for Disease Control and Prevention. The scope of this issues is growing with approximately 100 million people living with prediabetes or diabetes.[1] Unlike type 1 diabetes mellitus (T2DM) which is an autoimmune disease, type 2 diabetes (T2DM) is characterized by having high blood glucose (BG) as a result of insulin resistance or decreased insulin secretion.[1,2] The treatment of T2DM should include important lifestyle modification as well as pharmacological therapies. These interventions should be implemented quickly, as early treatment and correction of elevated BG can greatly reduce macrovascular events such as heart attacks and strokes, and microvascular disease such as neuropathy, nephropathy and retinopathy.[2]

According to the American Diabetes Association (ADA) and The American Association of Clinical Endocrinologists (AACE), the initial pharmacological treatment for type 2 diabetes is metformin followed by a second agent, such as a glucagon-like-peptide 1 agonist (GLP-1), other oral therapies or insulin if hyperglycemia and/or A1c remain.[3] All pharmacological therapies should be accompanied by appropriate lifestyle changes to help reduce BG levels. GLP-1 agonists have been shown through many clinical trials to achieve glycemic control as an add-on to metformin while promoting weight loss and decreasing the risks of hypoglycemia.[5,6,7,8,9,10,11] There are currently 6 FDA approved GLP-1 agonists on the market for the indication of diabetes. These medications are differing in efficacy, administration times, tolerability and cost. On December 5, 2017 the latest GLP-1 agonist Semaglutide (Ozempic) was approved by the FDA for use in adults with type 2 diabetes as an add on to metformin along with diet and exercise.[4] The purpose of this article is to review the pharmacology, pharmacokinetics, clinical trials, adverse events and the dosing of semaglutide in the treatment of T2DM.

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Pharmacology

Semaglutide is a GLP-1 agonist that activates the GLP-1 receptors and mimics the incretin effects in the body. GLP-1 and gastric inhibitory polypeptide (GIP) are incretin hormones in that mediate insulin secretion in the presence of elevated glucose.[4] GLP-1 agonists promote insulin secretion by the beta cells of the pancreas leading to an increase of glucose uptake by the muscles, decreased glucagon secretion, and slowed gastric emptying.[4]

Semaglutide was derived from liraglutide with a few changes made to its molecule. One of the changes included changing Ala in its position 8 to alpha-amino-iso-butyric acid (Aib) which would result in complete DPP-4 resistance.[4] This along with introducing a longer and more flexible linker would result in having an increased half-life of 165 hours compared to 12 hours for liraglutide. This longer half-life allows for its once weekly administration.[4] Once administered, the time to maximum concentration of semaglutide is 1 to 3 days with a steady state reached after 4 to 5 weeks.[4] The mean steady state concentrations of semaglutide 0.5 mg and 1 mg are approximately 65.0 ng/mL and 123.0 ng/mL, respectively.[4] When administered subcutaneously in the abdomen, thigh or upper arm, the results showed that there is a similar exposure to the drug in all the different sites.[4] Semaglutide is mainly eliminated by proteolytic cleavage of the peptide backbone and beta-oxidation of the fatty acid chain. Three percent of semiglutide and its metabolites are excreted unchanged in the urine and feces.[4] Semaglutide has a volume of distribution of 12.5 L with a clearance near 0.05 L/hr. The pharmacokinetics of semaglutide appear to be not affected by age, sex, and ethnicity, renal or hepatic impairment.[4] **Table 1** shows a summary of the pharmacokinetics of semaglutide.

Clinical Trials

Before being approved by the FDA, semaglutide completed 6 phase 3 clinical trials. Combined, these trials included more than 8000 adults with T2DM. These trials also included some patient with high cardiovascular risk and those with renal disease.[5-11] The SUSTAIN clinical trial series which compared semaglutide with placebo and active comparators such as exenatide ER, and insulin glargine. Results of the SUSTAINN trials will be discussed below and a summary of these trials may be seen in **Table 2.**[5-11]

SUSTAIN 1

SUSTAIN 1 was a 30 week randomized, double-blind, multicenter, multinational study that compared subcutaneous semaglutide 0.5 mg and 1.0 mg vs placebo.[5] This study included treatment-naïve patients with T2DM, age ≥18 years and an HbA1c level of 7-10%. Patients were required to have only been treated with diet and exercise for 30 days prior to the screening. The pa-

Table 1 | Semiglutide Pharmacokinetics[4]

Parameter	Value
Absorption	
Biovailability	89%
C_{max}	123.0 ng/mL
T_{max}	1-3 days
Distribution	
V_D	12.5 L
Protein Binding	>99% Albumin Bound
Metabolism	Proteolytic cleavage of peptide backbone and beta-oxidation of fatty acid side chane
Elimination	
Clearance	0.05 L/hour
Half-life	165 hours (~1 week)

C_{max} = maximum concentration; **L** = liter **mL** = milliliters; **ng** = nanograms; **T_{max}** = time to maximum plasma concentration; V_D = volume of distribution

tients studied had a mean age of 54 and had mean disease duration of 4.2 years, mean baseline HbA1c of 8.05%, and mean baseline bodyweight of 91.93 kg. Patients were randomized assigned to receive once weekly dosing of subcutaneous semaglutide 0.5 mg (n =128), 1.0 mg (n=130) or volume matched subcutaneous placebo (n=129). Patients were given 0.25 mg once weekly injections for 4 weeks, then escalated to 0.5 mg for the rest of the study or 0.25 mg for 4 weeks, followed by the 0.5 mg for another 4 weeks, then escalated to 1.0 mg dose for the rest of the study. The primary endpoint was the change in mean HbA1c from baseline after 30 weeks. Change from baseline mean HbA1c treatment difference with semaglutide 0.5 mg vs placebo was -1.43 (95% CI [-1.71 to -1.15] and the treatment difference with semaglutide 1 mg vs placebo was -1.53 (95%[-1.81 to -1.25]. Secondary outcomes also favored semaglutide, with mean body weight reduced -3.73 kg (95% CI [-4.54 to -2.91]) and -4.53 kg (95% CI [-5.34 to -3.72])-in semaglutide 0.5 mg and 1.0 mg treated patients, respectively, compared to a 0.98 kg loss with placebo ($p<0.0001$ for both groups). Other secondary endpoints included change in fasting blood glucose (FBG) levels, change in systolic and diastolic blood pressure, and subjects who achieved HbA1c below 7.0% and 6.5%. FBG decreased by a mean of -2.41 mmol/L in semaglutide 0.5 mg, -2.39 mmol/L in semaglutide 1 mg and -0.55 mmol/L in the placebo group. Systolic blood pressure (SBP) decreased by a mean of -2.29 mmHg in semaglutide 05 mg, -2.74 mmHg in semaglutide 1 mg and -2.01 mmHg in placebo. Diastolic blood pressure (DBP) decreased by -0.73 mmHg in semaglutide 0.5 mg and it increased by a mean of 0.22 mmHg in semaglutide 1 mg and a mean increase of 0.60 mmHg in placebo. A greater proportion of patients receiving semaglutide 0.5 mg and 1.0 mg achieved the HbA1c targets of <7% with 74% of semaglutide 0.5 mg and 72% of semaglutide 1 mg vs 25% with placebo, $p<0.0001$. In the study, 17 people (13%) assigned to 0.5 mg semaglutide, 16 people (12%) assigned to 1.0 mg semaglutide and 14 people (11%) assigned to placebo discontinued treatment due to gastrointestinal (GI) adverse events such as nausea and diarrhea. In this study, no deaths were reported and most of the reported adverse events were mild to moderate severity. Nausea was reported by 26 people who received the 0.5 mg, 31 people who received the 1.0 mg and 10 people that received placebo.[5]

SUSTAIN 2

The SUSTAIN 2 trial was a 56 week phase 3a, randomized, double-blind, multinational, multicenter trial that compared semaglutide 0.5 mg and 1.0 mg to sitagliptin 100mg as add-on therapy in patients with type 2 diabetes.[6] The study included patients aged ≥18 years with type 2 diabetes and an HbA1c between 7% and 10.5%, which is a higher range than in SUSTAIN 1. For 90 days before screening, the patients received stable doses of metformin, pioglitazone, rosiglitazone or metformin combined with a thiazolidinedione (TZD). This included metformin dosage ≥1500 mg, pioglitazone ≥30 mg, or rosiglitazone ≥4 mg. The study included 4 treatment groups randomized into either semaglutide 0.5 mg plus sitagliptin placebo, semaglutide 1 mg plus sitagliptin placebo, sitagliptin 100 mg plus semaglutide 0.5 mg placebo, or sitagliptin 100 mg plus semaglutide 1 mg placebo. The semaglutide injections followed a fixed dose escalation regimen as in SUSTAIN 1, and the tablets were taken once daily. In the study, 409 patients received semaglutide 0.5 mg, 409 received semaglutide 1 mg and 407 received sitaglipitin 100 mg.

Mean HbA1c at baseline was 8.1% and mean weight at baseline was 89.5 kg. The primary endpoint of the study was the change in HbA1c from baseline at week 56. By week 56, add-on injectable semaglutide was superior to oral sitagliptin in reduction from baseline HbA1c.[6] The results showed a 1.3% reduction in HbA1c in semaglutide 0.5 mg, 1.6% in semaglutide 1.0 mg and 0.5% with sitagliptin. The estimated treatment difference compared to sitagliptin was -0.77% (95% CI [-0.92 to -0.62]) with semaglutide 0.5 mg and -1.06% (95% CI [-1.21 to 0.91]) in semaglutide 1 mg.[6] Change in body weight was also significantly reduced with semaglutide 0.5 and 1 mg with a mean reduction of -4.3 kg and -6.1 kg, respectively, compared to -1.9 kg with sitagliptin ($p<0.0001$ for both comparisons to sitagliptin). When compared with sitagliptin, the semaglutide 0.5 mg weekly dose had a difference in weight -2.35 kg (95% CI [-3.06 to 1.63]) and the semaglutide 1 mg had a reduction of -4.20 kg (95% CI [-4.91 to -3.49]).[6] FBG decreased by a mean of -35 mg/dL in semaglutide 0.5mg, -43 mg/dL in semaglutide 1 mg and -23 mg/dL in sitagliptin.

Additionally, a greater proportion of patients on the semaglutide 0.5 and 1 mg achieved a HbA1c target of <7% with 69% of the semaglutide 0.5 mg dose and 78% with semaglutide 1 mg compared to only 36% with sitagliptin 100 mg. Just like with SUSTAIN 1, the main adverse events were gastrointestinal in nature, including nausea and diarrhea. In the study 33 patients (8%) of semaglutide 0.5 mg, 39 patients (10%) of semaglutide 1.0 mg, and 12 patients (3%) of sitagliptin discontinued treatment.[6] Nausea was reported by 73 patients that received semaglutide 0.5 mg, 72 patients that received semaglutide 1 mg, and 30 patients that received placebo. Diarrhea was reported by 54 patients in the semaglutide 0.5 mg group, by 53 patients of the semaglutide 1.0 mg group, and by 29 patients that received placebo.[6]

SUSTAIN 3

Similar to the previously reviewed trials, SUSTAIN 3 is a randomized, multicenter, multinational, double blind phase 3a study, that compared semaglutide 1 mg once weekly (n=404) to exenatide extended-release (ER) 2 mg once weekly (n=405) in improving glycemic control in patients with T2DM. Enrolled patients required inadequate glycemic control with an HbA1c between 7.0% and 10.5%.[7] The patients studied were on stable doses of one or two oral antidiabetic drugs such as metformin (1500 mg or above), TZD (maximally tolerated dose), or sulfonylurea (maximally tolerated dose) for 90 days before the screening, and a mean disease duration of 9.2 years.[7] The mean baseline HbAc was 8.35% and mean baseline bodyweight was 95.79 kg. The patients were randomized to receive either weekly semaglutide 1 mg subcutaneously or exanetide ER 2 mg subcutaneously with a dose titration as previously mentioned for the semaglutide group. Exenatide ER, however, was given the same 2 mg dose for the whole 56 weeks. The primary outcome of the study was HbA1c reduction from baseline at 56 weeks. Add-on semaglutide 1 mg was superior to add-on exenatide ER 2 mg with a HbA1c decrease of -1.5% vs -0.9%, respectively, with a difference of -0.62% (95% CI [-0.80 to -0.44]).[7] Body weight decreased -5.6 kg with semaglutide vs -1.9 kg decrease in exenatide ER with an estimated treatment different of -3.78 kg (95% CI [-4.58 to -2.98]).[7] Other secondary outcomes were change in FBG, change in blood pressure, and proportion of patients having a HbA1c of <6.5% or 7.0%. FBG decreased by a mean of 51.22 mg/dL in semaglutide 1 mg and 36.1 mg/dL in the exenatide 2 mg group. SBP decreased by a mean of 4.6 mm Hg in semaglutide 1 mg and a mean of 2.23 mmHg in exenatide 2 mg. DBP decreased by a mean of 1.0 mmHg in semaglutide 1 mg and 0.1 mmHg in the exenatide group. Rates of achieving a HbA1c target of <7% at the end of the study was seen at 67% in semaglutide group vs 40% in the exanetide group. Similarly, this study also showed GI adverse events being more common in the semaglutide group, but with more injection site reactions with the exenatide group. In the study 32 of the patients in semaglutide group and 38 patients in the exenatide group discontinued the study due to side effects.[7] GI side effects were reported by 41.8% of patients in the semaglutide treatment and 33.3% of exenatide ER patients.[7]

SUSTAIN 4

The SUSTAIN 4 trial analyzed patients 18 and older, with type 2 diabetes and inadequate glycemic control with a HbA1c between 7.0 and 10.0%.[8] The patients were insulin-naïve and being treated with a stable dose of metformin alone (1500 mg or higher) or in combination with a sulfonylurea (half of maximum allowed dose or higher), for at least 90 days before the screening. Mean HbA1c at baseline was 8.17% and mean bodyweight at baseline was 93.45 kg. The patients had a mean disease duration of 13.3 years.[8] The study compared once weekly dose of subcutaneous semaglutide 0.5 mg (n=362) or 1 mg (n=360) to subcutaneous once daily dose of insulin glargine (n=360).[8] In this study the methods of dose administration and dose escalation for semaglutide remained the same as in the other SUSTAIN studies and insulin glargine was given as 10 units once daily then adjusted to achieve a fasting plasma glucose of 71-100 mg/dL. The primary outcome of the study was the change in mean HbA1c from baseline to week 30. Semaglutide 0.5 mg and 1 mg significantly improved HbA1cwith a mean decreased change of -1.21% (95% CI [1.10 to 1.31]) and -1.64% (95% CI [1.54 to 1.74]), respectively, compared to -0.83% (95% CI [0.73 to 0.93]) decrease with insulin glargine.[8] The study also looked at change in body weight, change in FBG, change in blood pressure, and patients achieving goal HbA1c. Semaglutide 0.5 mg and 1 mg significantly reduced mean body weight with a decrease of -3.47 kg (95% CI [3.00 to 2.93]) and -5.17 kg (95% CI [4.71 to 5.66]), compared to an increase of +1.15 kg (95% CI [0.70 to 1.61]) insulin glargine. FBG decreased by a mean of -36.74 mg/dL in semaglutide 0.5 mg, -49.21 mg/dL in semaglutide 1 mg and -38.18 mg/dL in the insulin glargine group.[8] SBP decreased by a mean of -4.65 mmHg in semaglutide 0.5 mg, -5.17 mmHg in semaglutide 1 mg and -1.68 mmHg in the insulin glargine group. DBP decreased by a mean of -1.38 mmHg in semaglutide 0.5 mg, -0.98 mmHg in semaglutide 1 mg and -1.44 mmHg in insulin glargine. A significantly greater proportion of semaglutide patients achieved HbA1c target of <7.0% at 57% in the 0.5 mg semaglutide arm and 73% in the1 mg semaglutide arm. This compared to only 38% of insulin glargine patients. Six deaths were reported with this study, which included 5 cardiovascular deaths and one pancreatic carcinoma. This could possibly be related to the administration of semaglutide however causality cannot be determined. Similarly adverse events reported were nausea, diarrhea, and hypoglycemia. Nausea was reported in 77 patients receiving 0.5 mg, in 80 patients receiving the 1 mg semaglutide, and in 12 patients receiving insulin glargine.[8]

SUSTAIN 5

SUSTAIN 5 was a 30 week, double-blind study that tested the safety and efficacy of semaglutide as add-on therapy to 397 patients with uncontrolled diabetes with a stable dose of basal insulin with or without metformin.[9] Subjects were considered to be on stable diabetes treatment with a dose of 0.25 units/kg/day or 20 units/day of insulin glargine, detemir, degludec and/or NPH, either alone or with metformin 1500mg/day or above, for 90 days before the screening. Mean baseline HbA1c of all patients was 8.37% and mean body weight of all patients was 91.70 kg. The primary outcome was change in HbA1c from baseline at week 30. The study showed that HbA1c levels were significantly reduced by -1.4% with semaglutide 0.5 mg (n=133) and 1.8% with 1 mg (n=132) once weekly compared with +0.1% increase with placebo (n=131) despite their ongoing treatment with basal insulin +/- metformin.[9] The estimated treatment difference (ETD) vs placebo was -1.35% (95% CI [-1.61 to -1.10]) with semaglutide 0.5 mg and -1.75% (95% CI [-2.01 to -1.50]) with semaglutide 1mg.[9] Like the previous trials, semaglutide 0.5 mg and 1mg groups found a weight loss of -3.7 kg and -6.4 kg, respectively, vs 1.4 kg loss with placebo with a difference of -2.31 kg (95% CI [-3.33 to -1.29kg]) with semaglutide 0.5 mg and -5.06 kg (95% CI [-6.08 to -4.04kg]) for semaglutide 1mg.[9] This study had the same secondary outcomes as the previous trials, which showed similar improvement in FBG and blood pressure as the previous trials with the semaglutide treated patients. FBG decreased by a mean of -29.14mg/dL in semaglutide 0.5 mg, -42.38 mg/dL in semaglutide 1 mg and -8.51 mg/dL in placebo. SBP decreased by a mean of -4.29 mmHg in semaglutide 0.5 mg, -7.27 mmHg in semaglutide 1 mg and -0.99 mmHg in placebo. DBP decreased by a mean of -1.84 in semaglutide 0.5 mg, -1.50 mmHg in semaglutide 1 mg and -2.17 mmHg in placebo. Additionally, the main side effects were GI disorders which led to premature discontinuation in 5 people of semaglutide 0.5 mg, 5 people of 1 mg and 7 people from the placebo group.[9]

SUSTAIN 6

SUSTAIN 6 was a large (n=3297), 104 week, phase 3, double

Table 2 | Summary of the SUSTAIN Trial Series Primary Outcomes

Trial	Interventions	Background Therapy	Primary Outcome	Results: ΔHbA1c (95% CI)
SUSTAIN 1	• SEM 0.5 mg (n=128) • SEM 1.0 mg (n=130) • Placebo (n=129)	None	Change in HbA1c from baseline at 30 weeks	**ETD between SEM 0.5 mg and Placebo** • -1.43% (-1.71 to –1.15%) **ETD between SEM 1.0 mg and Placebo** • -1.53% (-1.81 to –1.25%)
SUSTAIN 2	• SEM 0.5 mg (n=409) • SEM 1.0 mg (n=409) • Sitagliptin 100 mg (n=407)	MET, TZD, or both[a]	Change in HbA1c from baseline at 56 weeks	**ETD between SEM 0.5 mg and Sitagliptin** • -0.77% (-0.92 to –0.62%) **ETD between SEM 1.0 mg and Sitagliptin** • -1.06% (-1.21 to –0.91%)
SUSTAIN 3	• SEM 1.0 mg (n=404) • EXEN-ER 2.0 mg (n=405)	MET, TZD, or both[a]	Change in HbA1c from baseline at 56 weeks	**ETD vs EXEN-ER** • -0.62% (-0.80 to –0.44%)
SUSTAIN 4	• SEM 0.5 mg (n=362) • SEM 1.0 mg (n=360) • Glargine (n=360)	Met with or without SU[b]	Change in HbA1c from baseline at 30 weeks	**ETD between SEM 0.5 mg and Glargine** • -0.38% (-0.52 to –0.24%) **ETD between SEM 1.0 mg and Glargine** • -0.41% (-0.96 to –0.67%)
SUSTAIN 5	• SEM 0.5 mg (n=128) • SEM 1.0 mg (n=130) • Placebo (n=129)	Basal insulin with or without MET[c]	Change in HbA1c from baseline at 30 weeks	**ETD between SEM 0.5 mg and Placebo** • -1.35% (-1.61 to –1.10%) **ETD between SEM 1.0 mg and Placebo** • -1.75% (-2.01 to –1.50%)
SUSTAIN 7	• SEM 0.5 mg (n=301) • SEM 1.0 mg (n=300) • DUL 0.75 mg (n=299) • DUL 1.5 mg (n=299)	MET[d]	Change in HbA1c from baseline at 40 weeks	**ETD between SEM 0.5 mg and DUL 0.75 mg** • -0.40% (-0.55 to –0.25%) **ETD between SEM 1.0 mg and DUL 1.5 mg** • -0.41% (-0.57 to –0.25%)

DUL = dulaglutide; **ETD** = estimated treatment difference; **EXEN-ER** = exenatide extended release; **HbA1c** = hemoglobin A1C; **MET** = metformin; mg = milligram; **SEM** = semaglutide; **SU** = sulfonylurea; **TZD** = thiazolidinedione

a: Patients were receiving stable doses of other oral antidiabetic agent for 90 days prior to study

b: Patients were insulin naïve, on a stable dose of metformin +/- sulfonylurea for 90 days prior to study

c: Patients were on stable dose of basal insulin +/- metformin

d: Metformin dose and duration of therapy was not reported

-blind, randomized, placebo-controlled, multicenter, multinational study to determine the safety of semaglutide and evaluate cardiovascular (CV) and long term outcomes in patients with T2DM and a HbA1c >7%.[10]

The study included patients 50 years and older with cardiovascular disease (CVD), chronic heart failure (NYHA class II or III), and stage 3 or greater chronic kidney disease (CKD). The study also included patients that were 60 years and older with at least one CVD risk factor. This study excluded patients that were on any DPP-4 inhibitors within 30 days before the screening, GLP-1 agonists use, or insulin (other than the basal or premixed) with 90 days before the screening.[10] Methods of dose administration and escalation were the same as in the other SUSTAIN trials. Patients were randomized in a 1:1:1:1 ratio for the 4 interventions of semaglutide 0.5 mg and 1 mg, and placebo 0.5 mg and 1 mg.

The primary outcome was the first occurrence of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke. At baseline 83% (n=2735) of patients had either CVD, CKD, or both. The primary outcome occurred in 6.6% of semaglutide groups and in 8.9% of placebo group (Hazard Ratio=0.74, 95% CI [0.58 to 0.95], p<0.001 for noninferiority).[10] Nonfatal MI occurred in 2.9% of patients receiving semaglutide and in 3.9% of patients receiving placebo with a HR=0.74 (95% CI [0.51 to 1.08], p=0.12). Nonfatal stroke occurred in 1.6% of patients receiving semaglutide and 2.7% of patients receiving placebo with a HR of 0.61 (95% CI [0.38 to 0.99], p=0.04).[10] The rates of death from CV causes were similar among the 2 groups. The semaglutide group showed lower rates of new or worsening nephropathy but higher rates of retinopathy complications such as blindness and vitreous hemorrhage with a HR of 1.76 (95% CI [1.11 to 2.78], p = 0.02).[10] The authors concluded that in patients with type 2 diabetes who were at high CV risk, the rates of CV death, nonfatal MI or stroke was non-inferior to standard of care with a possibility of reduction in those taking semaglutide.[10]

SUSTAIN 7

The latest trial published in the SUSTAIN series is SUSTAIN 7. This is a phase 3, randomized, double blind, multicenter, multinational study that compared semaglutide and dulaglutide in 1199 patients with poorly controlled T2DM previously taking metformin monotherapy.[11] Included patients were 18 years and older with a HbA1c of 7.0-10.5% and with a stable dose of metformin with a dosage 1500 mg or maximal tolerated dose. Mean HbA1c at baseline was 8.2% and mean body weight at baseline was 95.2 kg. Patients were randomly assigned to receive semaglutide 0.5 mg (n=301), semaglutide 1mg (n=300), dulaglutide 0.75 mg (n=300), or dulaglutide 1.5 mg (n=300). Patients that were to receive semaglutide 0.5 mg were receiving the 0.25 mg dose for 4 weeks, then the 0.5 mg for the remainder of the study. Patients that were receiving the semaglutide 1mg received the 0.25 mg dose for 4 weeks, then the 0.5 mg dose for 4 weeks, then the 1mg dose for the remainder of the study. The dulaglutide patients received the same dose through the whole study.

The primary outcome of the study was change of mean HbA1c from baseline at week 40. HbA1c reduced by -1.51% in the semaglutide 0.5 mg, -1.78% in the semaglutide 1 mg group, -1.11% in the duleglutide 0.75 mg group, and -1.37% in the dulaglutide 1.5 mg group. The estimated treatment difference between semaglutide 0.5 mg and dulaglutide 0.75 mg was -0.40% (95% CI [-0.55 to -0.25%]). The estimated treatment difference between semaglutide 1 mg and dulaglutide 1.5 mg was -0.41% (95% CI [-0.57 to -0.25%]).[11]

One secondary outcome was weight loss, which was also significantly decreased in the semaglutide patients with mean -4.56 kg in semaglutide 0.5 mg, -6.53 kg in semaglutide 1mg, -2.30 kg in dulaglutide 0.75 mg and -2.98 kg in dulaglutide 1.5 mg. The estimated weight loss difference between semaglutide 0.5 mg and dulaglutide 0.75 mg was -2.26 kg (95% CI [-3.02 to -1.51 kg]). The estimated weight loss difference between semaglutide 1 mg and dulaglutide 1.5 mg was -3.55 kg (95% CI [-4.32 to -2.78 kg]), p <0.0001.[11] Other secondary endpoints included change in FBG and change in BP. FBG decreased by a mean of -2.18 mmol/L in semaglutide 0.5 mg, -2.83 mmol/L in semaglutide 1 mg, -1.87 mmol/L in dulaglutide 0.75 mg and -2.25 in dulaglutide 1.5 mg. SBP decreased by a mean of -2.44 mmHg in semaglutide 0.5 mg, -4.88 mmHg in semaglutide 1 mg, -2.16 mmHg in dulaglutide 0.75 mg and -2.86 mmHg in dulaglutide 1.5 mg. DBP decreased by a mean of -0.57 mmHg in semaglutide 0.5 mg, -2.05 mmHg in semaglutide 1 mg, -0.35 mmHg in dulaglutide 0.75 mg and -0.03 in dulaglutide 1.5 mg. Overall there was a higher proportion of patients achieving an HbA1c < 7.0%, with 79% of the semaglutide patients and 67% of the dulaglutide patients. Similar to the other SUSTAIN trials, gastrointestinal disorders were the most common adverse event. There were also six deaths, one in each semaglutide group and 2 in each dulaglutide group. Additionally, 22 patients in the semaglutide 0.5 mg, 21 patients in the semaglutide 1 mg, 13 patients in the dulaglutide 0.75 mg and 16 patients in the dulaglutide 1.5 mg group did not complete the study, whether it was because they chose to withdrawal do to ADE, they were lost to follow-up, or death.[11]

Adverse Events and Precautions

The common adverse effects associated with semaglutide are nausea, vomiting, diarrhea and abdominal pain[4]. **Table 3** shows the frequency of these adverse effects in the studied clinical trials. Nausea, vomiting and diarrhea were the most common side effects leading to treatment discontinuation.[5,6,7,8,9,11] Additionally, semaglutide may increase the risks of hypoglycemia but the incidence is higher in patients that are being treated with insulin or a sulfonylurea as well.[4] In SUSTAIN 2, when compared with sitagliptin, there were a total of 9 patients that reported hypoglycemia from the treatment group (7 cases in semaglutide 0.5 mg, 2 cases in semaglutide 1.0 mg, and 5 in the sitagliptin group).[6] In SUSTAIN 4, when compared to insulin glargine, severe hypoglycemia was reported by 16 patients in the 0.5 mg semaglutide and 20 patients in the 1.0 mg semaglutide compared to 38 patients being treated with the insulin glargine.[9]

Semaglutide has shown a dose-dependent increase in the incidence of thyroid C-cell tumors in mice and rats.[4] Although it is unknown whether it causes thyroid C-cell tumors in humans, semaglutide is contraindicated if the patients has a personal or family history of medullary thyroid carcinoma (MTC) or Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). [4] Additionally, acute pancreatitis was confirmed in 7 treated patients (0.3 cases per 100 patient years) versus 3 comparator treated patients (0.2 cases per 100 patient years), and therefore patients should look for signs and symptoms of pancreatitis including abdominal pain and vomiting if being initiated with semaglutide[4]. Lastly, in the 2-year trial SUSTAIN 6, semaglutide showed more complications with diabetic retinopathy (3.0%) compared to placebo (1.8%), so it is important to assess the worsening progression of retinopathy if prescribing semaglutide.[4]

DOSING, ADMINISTRATION, AND COST

Semaglutide is a once weekly subcutaneous injection that is available in pre-filled 3 mL pen with concentration of 2 mg/1.5 mL.[4] The initial dose is 0.25 mg once weekly for 4 weeks, then increased to 0.5 mg once weekly.[4] The 0.25 mg is only intended for treatment initiation due to increased gastrointestinal side effects if a higher dose is initiated. After 4 weeks of the 0.5 mg dose, semaglutide may be increased to 1 mg weekly if additional glycemic control is needed.[4] With a weekly maintenance dose of 1 mg a patient would need 1 pen per month. Semaglutide can be injected in the abdomen, thigh, or upper arm with no dose adjustments for patients with renal or hepatic impairment.[4] If a dose is missed it may be administered within 5 days of the missed dose. The unopened semaglutide pens can be stored in the refrigerator, but once opened the pens can be stored at room temperature for 56 days. No clinically relevant drug-drug interactions were found with semaglutide, however since it delays gastric emptying it could impact the absorption of other oral medications. Additionally, if co-administered with insulin or a sulfonylurea, it is important to lower the dose of the semaglutide to prevent hypoglycemia.[4] Currently, Novo Nordisk™ offers a prescription savings assistance program for patients with commercial insurance. The savings program provides a maximum of $150 deductions per prescription, and patients can pay as little as $25.[12]

SEMAGLUTIDE AND OTHER GLP-1 RAS

There has been an increase in GLP-1 agonists in the market that differ in half-life, tolerability, cost and dosing frequency. As a class, the GLP-1 agonists have been shown to lower HbA1c and reduce weight with a low risk of hypoglycemia. Currently, semaglutide has been shown to be the better at lowering HgA1c and promoting weight loss when compared to sitagliptin, exanetide, insulin glargine and dulaglutide. Semaglutide also has an oral product that is in the process of being approved by the FDA, which could also be used in patients that want therapy that does not include needles. Furthermore, semaglutide is also the only other GLP-1 agonist besides liraglutide that will be indicated for weight loss. Additionally, an oral formulation of semaglutide is under investigation and results for most clinical trials should be available sometime during 2019 (***NCT02906930***).

CONCLUSIONS

Semaglutide is the newest GLP-1 receptor agonist approved for the treatment of type 2 diabetes in addition to diet and exercise in patients that are 18 YOA and older.[4] The SUSTAIN clinical trials demonstrated semaglutide's ability to reduce HbA1c compared to placebo, non insulin therapies, and insulin therapies.[5,6,7,11]. Not only was this reduction in HbA1c seen, it also allowed for many patient to achieve their target A1c levels as well as weight loss for those using this therapy. Semaglutide has demonstrated cardiovascular safety in patients with established cardiovascular disease and looks promising for beneficial outcomes; however, further trials are required by the FDA to establish cardiovascular benefit.

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Table 3 | Summary of Overall SUSTAIN 1-5 Trial Gastrointestinal Adverse Event Incidence

Interventions	Total patients with events[b] (SAEs)[c]	Nausea	Diarrhea	Vomiting
• SEM 0.5 mg (n=823) • SEM 1.0 mg (n=819) • Placebo (n=1644)	• 52% (3.5%) • 50.4% (4.4%) • 34.3% (2.4%)	• 17.3% • 21.7% • 7.7%	• 17.6% • 21.7% • 10.8%	• 10.2% • 14.5% • 4.7%
• SEM 0.5 mg (n=1373) • SEM 1.0 mg (n=1373) • Non-GLP-1 RA comparator[a] (n=1252)	• 42.2% (1.3%) • 42.7% (0.5%) • 18.5% (0.5%)	• 16.8% • 19.2% • 4.8%	• 12.1% • 14.0% • 4.8%	• 6.3% • 8.6% • 2.5%
• SEM 1.0 mg (n=404) • EXEN-ER 2.0 mg (n=405)	• 41.8% (1.5%) • 33.3% (0.7%)	• 22.3% • 11.9%	• 11.4% • 8.4%	• 7.2% • 6.2%

EXEN-ER = exenatide extended release; **SAE** = serious adverse event; **SEM** = semaglutide
a: Non-glucagon like peptide-1 receptor antagonists comparators, specifically sitagliptin or glargine
b: Gastrointestinal events included (in order of highest to lowest incidence) nausea, diarrhea, vomiting, constipation, dyspepsia, abdominal discomfort, abdominal pain, eructation, gastroesophageal reflux disease, flatulence, dry mouth, toothache.
c: Serious adverse events were defined as death, a life-threatening experience, in-patient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, required intervention by a medical or surgical team

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