Brand Name: Ozempic

Generic Name: semaglutide

Manufacturer[1]: Novo Nordisk

Drug Class[2]: Glucagon-like peptide-1 (GLP-1) receptor agonist

Uses[1]: Labeled: Type 2 diabetes
Unlabeled: unknown

Mechanism of action[3]: A glucagon-like peptide 1 receptor (GLP-1) agonist that increases insulin production by the activation of adenylyl cyclase in the beta cells of the pancreas. As a GLP-1 agonist, it also goes to the brain to suppress appetite and slows the emptying of the stomach.

Pharmacokinetics[4]: half-life: 165-184 hours

Efficacy[4,5,6]:

Sorli C, Shin-ichi H, Tsoukas G, et al. Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomized, placebo-controlled, parallel-group, multinational, multicenter phase 3a trial. Lancet Diabetes Endocrinology [serial online]. 2017. Available from: www.thelancet.com/diabetes-endocrinology. Accessed January 23, 2017.

Study design: double-blind, randomized, placebo-controlled, parallel-group, multinational, multicenter design study

Description of Study:
Methods: This trial was a multicenter study from 72 different sites in 8 different countries (USA, UK, Canada, Mexico, Italy, Japan, Russia, and South Africa). The majority of the sites were in the United States. Notable inclusion criteria consisted of being 18 years or older, a diagnosis of type II diabetes, diet and exercise as the only means of blood glucose control for at least the 30 days prior to the screening visit, and an HbA1c between 7-10%. Three hundred eighty eight patients were randomized to either receive 0.5 mg of semaglutide, 1.0 mg of semaglutide, 0.5 mg of placebo, or 1.0 mg of placebo in a 2:2:1:1 ratio. The duration of the study was 30 weeks. Both semaglutide and the placebo were given to the patients in pre-filled pen-injectors. The patients were instructed to inject the treatment once weekly in the same place on the body and on the same day each week so that the treatment was seven days apart. Efficacy and safety was measured. Any patient receiving a minimum of one dose of either semaglutide or placebo were included in the analysis. The primary and secondary endpoints assessed from baseline to 30 weeks were the mean change of HbA1c and the mean change of weight respectively.
Results: The primary endpoint was achieved with a -1.45% difference seen from baseline for a 0.5 mg dose of semaglutide with a difference between 0.5 mg semaglutide and 0.5 mg placebo to be -1.43% ($p<0.0001$). For a 1.0 mg of semaglutide, the difference from baseline was 1.55% with the difference between 1.0 mg semaglutide and 1.0 mg placebo being -1.53% ($p<0.0001$). For the secondary endpoint, the difference from baseline in weight was -3.73 kg for 0.5 mg of semaglutide and a difference between 0.5 mg semaglutide to 0.5 mg placebo of -2.75 kg ($p<0.0001$). For 1.0 mg semaglutide, the difference in baseline for weight was -4.53 kg and the difference between 1.0 mg of semaglutide and 1.0 mg of placebo was -3.56 kg ($p<0.0001$). The results for placebo between baseline and 30 weeks for both the

primary and secondary endpoints were not statistically significant at -0.02% and -0.98 kg respectively. No deaths occurred throughout the study. Adverse effects mostly consisted of nausea and diarrhea.

Limitations: The limitations in this study were a short study duration of only 30 weeks, the 1.0 mg semaglutide group having a disproportionate increase in males (62%) along with a higher BMI averaging 33.92 kg/m^2, nonstandardization in terms of what time during the day the treatments were administered and how close to food intake the treatments were administered. The need to administer either metformin or other non-GLP-1 receptor agonists or non-DPP-4 inhibitors was a limitation for the placebo group. Since this study administered semaglutide as a monotherapy, a clinical limitation exists since under current type II diabetes management guidelines, metformin still remains as first line monotherapy. Other agents such as semaglutide was be added in addition to the existing metformin.

Conclusion: Semaglutide administered in doses of both 0.5 mg and 1.0 mg was statistically and clinically significant for lowering HbA1c and bodyweight within a 30 week time frame. Its novel once a week dosing regimen may be advantageous for both clinicians and patients who strive for both enhanced blood glucose control and compliance. Additionally, semaglutide was shown to be both safe and tolerable with the major adverse effects being nausea and diarrhea.

Marso S, Bain S, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. The New England Journal of Medicine. 2016;375(19);1834-1844.

Study design: double-blind, randomized, placebo-controlled, parallel-group, multinational, multicenter design study

Description of Study:
Methods: This study was conducted in 230 sites among 20 different countries. Notable inclusion criteria included an age greater than or equal to 50 years, a diagnosis of type II diabetes, a HbA1c of greater than or equal to 7%, never been on an injectable antidiabetic drug, taking two or less of any oral antidiabetic drug, and have either chronic heart failure, a specified level of chronic kidney disease, or cardiovascular dysfunction. Notable exclusion criteria consisted of being on a DPP-4 inhibitor within the past 30 days before the screening visit, any GLP-1 receptor agonists taken 90 days before the screening visit, and any cardiovascular events occurring 90 days prior to being randomized into groups. Three thousand two hundred ninety-seven patients were randomized to receive a 0.5 mg dose of either semaglutide or placebo or a 1.0 mg dose of either semaglutide or placebo in a 1:1:1:1 ratio. The primary outcome was the first incidence of cardiovascular mortality, myocardial infarction not resulting in mortality, and stroke not resulting in mortality. The study duration was for 104 weeks from 2013 through 2016 with a follow up period of 5 weeks.
Results: The primary cardiovascular outcome was displayed in 6.6% of patients taking semaglutide and 8.9% patients taking placebo with a p value of < 0.001 for noninferiority and 0.02 for superiority. Cardiovascular deaths occurred in 2.7% of patients taking semaglutide and 2.8% of patients taking placebo. The HbA1c was decreased by -1.1% and -1.4% for the 0.5 mg and 1.0 mg of semaglutide respectively from baseline to 104 weeks while the placebo had a decrease of -0.4% in both the 0.5 mg and 1.0 mg doses. When comparing semaglutide to placebo, the difference was -0.7% and -1.0% for the 0.5 mg and 1.0 mg groups respectively ($p<0.001$ for both 0.5 mg and 1.0 mg groups). Weight was decreased by -3.6 kg and -4.9 kg for the 0.5 mg and 1.0 mg of semaglutide respectively from baseline to 104 weeks while the placebo had a decrease of -0.7 kg and -0.5 kg in the 0.5 mg and 1.0 mg doses respectively. When comparing semaglutide to placebo, the difference was -2.9 kg and -4.3 kg for the 0.5 mg and 1.0 mg groups respectively ($p<0.001$ for both 0.5 mg and 1.0 mg groups). Retinopathy was also

statistically significant at a p value of 0.02 (3% occurring for the semaglutide group versus 1.8% for the placebo group). Nephropathy was also statistically significant at a p value of 0.005 (3.8% occurring in the semaglutide group versus 6.1% in the placebo group).

Limitations: The short duration of the study of 104 weeks to detect cardiovascular outcomes was a potential limitation in this study. Another limitation was the inability to determine what caused the actual decrease in the primary cardiovascular outcomes in the semaglutide group. A decrease in HbA1c, weight reduction, or other attributes of semaglutide may have caused the decrease in cardiovascular events.

Conclusion: The study did support the noninferiority of semaglutide for causing the first incidence of cardiovascular mortality, myocardial infarction not resulting in mortality, and stroke not resulting in mortality. Semaglutide also was shown to be safe and well tolerated with the majority of adverse effects being nonfatal gastrointestional effects. Semaglutide was shown to have a decreased risk of nephropathy and pancreatic cancer, while having an increased risk of diabetic retinopathy. Neither semaglutide nor the placebo group had any events of medullary thyroid carcinomas. Pancreatitis rates were equal among both the semaglutide and placebo groups and only occurred in 1 patient on 1.0 mg dose of semaglutide and two patients each on 0.5 mg and 1.0 mg of the placebo.

Nauck M, Petrie J, Sesti G, et al. A Phase 2, Randomized, Dose-Finding Study of the Novel Once-Weekly Human GLP-1 Analog, Semaglutide, Compared With Placebo and Open-Label Liraglutide in Patients With Type 2 Diabetes. Diabetes Care. 2016; 39:231-241.

Study Design: Randomized, double-blinded, placebo-controlled, parallel-group phase 2 study

Description of Study:
Methods: Four hundred fifteen patients were randomized into nine arms (semaglutide 0.1 mg once a week, semaglutide 0.2 mg once a week, semaglutide 0.4 mg once a week, semaglutide 0.8 mg once a week, semaglutide 0.8 mg once a week with dose up-titration, semaglutide 1.6 mg once a week with dose up-titration, open label liraglutide 1.2 mg once a day, liraglutide 1.8 mg once a day, and placebo). The study duration was 12 weeks. The study was conducted in 80 sites across 14 different countries outside of the United States. Key inclusion criteria were an age equal to or over 18 years, diagnosis of type 2 diabetes, previous treatment of only diet and exercise or diet and exercise combined with metformin, HbA1c between 7-10%, and weighed between 60-110 kg. Notable exclusion criteria consisted of being on antihyperglycemic medications with the exception of metformin, liver dysfunction, elevated serum creatinine, active cardiovascular dysfunction and retinopathy, and cancer (patients having basal and squamous skin cancer were not excluded). The primary endpoint was to detect a difference in HbA1c from baseline to week 12 and to determine the most safe and effacious dose to be further studied for the phase 3 trials. Secondary endpoints were to detect a difference in weight, safety, and tolerability from baseline to week 12.
Results: Statistically significant differences occurred for the reduction of HbA1c for the 0.2 mg dose of semaglutide versus placebo (difference of -0.4%), 0.4 mg dose of semaglutide versus placebo (difference of -0.6%), 0.8 mg versus placebo (difference of -1.0%), 0.8 mg dose of semaglutide with dose escalation versus placebo (difference of -1.0%), and 1.6 mg dose of semaglutide with dose escalation versus placebo (difference of -1.2%). Statistically significant differences occurred for the reduction of fasting plasma glucose semaglutide versus placebo for the 0.4 mg dose of semaglutide (difference of -1.2 mmol/L), 0.8 mg dose of semaglutide (difference of -2.0 mmol/L), 0.8 mg dose of semaglutide with dose

escalation (difference of -2.0 mmol/L), and 1.6 mg dose of semaglutide with dose escalation (difference of -2.1 mmol/L). Statistically significant differences occurred for the reduction in body weight for the semaglutide versus placebo for the 0.8 mg dose (difference of -2.2 kg), the 0.8 mg dose with dose escalation (difference of -2.4 kg), and the 1.6 mg dose with escalation (difference of -3.6 kg). The most frequent adverse effects were gastrointestinal (diarrhea, dyspepsia, nausea, and vomiting). Ten serious adverse events did occur being cardiovascular in nature. However, all the adverse events in the semaglutide groups were determined to not be caused by the treatment of semaglutide. The one patient who did have a serious adverse effect with liraglutide was determined to not have high probability that the adverse events occurred due to liraglutide. One serious adverse event did occur in the placebo group.

Limitations: The 12 week short duration of this study was a major limitation since glycated red blood cells turn over on average of every 17 weeks (120 days). Additionally, the safety profile is difficult to determine in such a short time span. Liraglutide being open label was also a limitation. Another limitation was that the study did not standardize for meal content or exercise duration or type.

Conclusion: Based of this dose finding study, the optimal dose of semaglutide was determined to be 0.5 mg and 1.0 mg once weekly. These two doses will be assessed for both safety and efficacy in the phase 3 trials. The safety and tolerability profile was positive with the major adverse effects being diarrhea, indigestion in the upper abdomen, nausea, and vomiting. Serious cardiovascular events occurring through the 12 weeks of the study was either deemed as having no or very little association to the study treatments.

Contraindications[4,7]:

Gastroporesis
Inflammatory bowel disease

Precautions[4,5,6,7]:

Precautions should exist in those with renal impairment.
Studies have only been conducted in the adult population. No studies have been conducted in the pediatric population.

Adverse effects[4,5,6,7]:

- GI disorders:
  - Nausea
  - Vomiting
  - Diarrhea
  - Dyspepsia
  - Constipation
- Nervous system disorders
  - Headache
  - Dizziness
  - Lethargy
- Infections/Infestations
  - Nasopharyngitis
  - Gastroenteritis
  - Urinary tract infection

General disorders and administration site conditions
    Fatigue
    Asthenia
Metabolism/nutrition disorders
    Anorexia
    Decreased appetite
Musculoskeletal/connective tissue disorders
Vascular disorders
    Hypertension
Injury/poisoning/procedural complications
Skin and subcutaneous disorders
Respiratory, thoracic, and mediastinal disorders
Eye disorders
    Diabetic retinopathy
Cardiac disorders
    Atrial fibrillation
Psychiatric disorders
Blood/lymphatic system disorders
Acute pancreatitis
Gallbladder disorder
    Cholelithiasis
    Acute cholecystitis
Acute renal failure
Allergic reaction
Injection-site reaction
Neoplasms

Drug Interactions: unavailable as of January 2017

Dosing/Administration[4,5,6]:

Adult dosing: 0.5 mg injected subcutaneously once a week (preferably on the same day every week) OR 1.0 mg injected subcutaneously once a week (preferably on the same day every week).

Use in special circumstances: unavailable as of January 2017

Conclusion[4,5,6,7]: Semaglutide 0.5 mg and 1.0 mg injected subcutaneously once a week is new GLP-1 receptor agonist that has the potential to be clinically useful as an additional antidiabetic therapy to the current first line agent, metformin. It also has potential benefits in patients who cannot tolerate metformin or who have problems maintaining a healthy BMI. Patients that struggle with adherence could also be greatly benefited by its once a week dosing. However, the potential risk of forgetting to take a once a week only dose could also pose problematic for compliance. The safety and tolerability of semaglutide also proves valuable with the main adverse effects being gastrointestinal in nature with nausea, vomiting, and diarrhea being the major effects. A major advantage is also that in clinical trials thus far, semaglutide has not shown to cause medullary thyroid cancer which is a black box warning for the GLP-1 agonist drug class. However, it will remain brand only for a significant period of time, and therefore, may be a more costly option. Additionally, the subcutaneous injection route is a disadvantage especially when compared to dipeptidyl peptidase 4 (DPP-4) inhibitors that can be taken

orally. However, DPP-4 inhibitors do not have the advantage of promoting weight loss. Further studies will have to be conducted and published before a superior benefit of semaglutide over other antidiabetic medications can be accessed. Additionally, three other once weekly GLP-1 receptor agonists (exenatide, albiglutide, and dulaglutide) will have to be evaluated against semaglutide. Albiglutide has the disadvantage of having to reconstitute the product before use, and exenatide ER has the disadvantage of being contraindicated in patients with end-stage renal failure. Dulaglutide, also with low dosage formulations of either 0.75 mg and 1.5 mg, will have to be compared against semaglutide to reveal the differences between the two drugs. Both are brand only, and thus, costly.

References:

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7. Prasad-Reddy L, Isaacs D. A clinical review of GLP-1 receptor agonists: efficacy and safety in diabetes and beyond. Drugs in Context. 2015;4:212283.

Prepared by: Jigna Richards, Doctor of Pharmacy Candidate