Key Paper Evaluation

Will oral semaglutide be used to reduce cardiovascular risk in subjects with type 2 diabetes instead of subcutaneous semaglutide?

Evaluation of Husain M, Birjebfeld AL, Donsmark M et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Eng J Med 2019;381:841-51.

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Abstract

Introduction: The ‘glutides’, which stimulate the glucagon-like peptide 1 (GLP-1) receptor to stimulate insulin secretion, are used in the treatment of type 2 diabetes. Semaglutide is the first glutide to be developed in an oral form. The PIONEER series of clinical trials (Peptide Innovation for Early Diabetes Treatment) were undertaken to establish a clinical role for oral semaglutide.

Areas covered: This evaluation is of PIONEER 6 in a non-inferiority phase 3a trial. In PIONEER 6, the primary outcome was the time from randomisation to first occurrence of a major adverse cardiovascular event and this was non-inferior with oral semaglutide, compared to placebo.

Expert opinion: In my opinion, there are several reasons why once-daily oral semaglutide may not replace once-weekly subcutaneous semaglutide in the treatment of type 2 diabetes. Most importantly, subcutaneous semaglutide has already been shown to be superior to placebo in reducing cardiovascular risk, whereas the study of this with oral semaglutide will not be completed until 2024. Secondly, it is debatable whether subjects will find the daily protocol for taking oral semaglutide more convenient than that for the weekly subcutaneous formulation.

Key words clinical trial, oral semaglutide, PIONEER, subcutaneous semaglutide, type 2 diabetes
1. Introduction

In the USA, the prevalence of type 2 diabetes has increased from 8.8% in 1999/2000 to 11.7% in 2013/4 with the increase being limited to individuals with abdominal obesity and those aged ≥ 45 years [2]. Despite the treatments available for type 2 diabetes, about two thirds of the subjects die from heart disease or stroke. Diabetes is also a leading cause of blindness, end-stage kidney failure, and lower limb amputations [3]. Clearly, there is a need for improved treatments for type 2 diabetes, and any new medicines that reduce cardiovascular outcomes will have a huge impact.

GLP-1 is produced by the gut, and in a glucose-dependent manner stimulates insulin secretion while inhibiting glucagon secretion, reduces appetite and energy intake, and delays gastric emptying. The ‘glutides’, which stimulate the glucagon-like peptide 1 (GLP-1) receptor, are used in the treatment of type 2 diabetes. Subcutaneous exenatide was the first GLP-1R agonist to be approved by the FDA for use in the treatment of type 2 diabetes. Although exenatide was approved in 2005, it wasn’t until 2017 that the clinical outcomes study was published showing no benefit on cardiovascular outcomes in subjects with type 2 diabetes [4]. In this interval other subcutaneous GLP-1R agonists had been developed, and three of them (liraglutide [5], semaglutide [6]) and albiglutide [7]) have been shown to have cardiovascular benefits, whereas lixisenatide did not [8].

Semaglutide is the first glutide to be developed in an oral form. It is co-formulated with the absorption enhancer sodium N-[8-(2-hydroxylbenzoyl) amino] caprylate (SNAC). SNAC increases localised pH, which increases solubility and protection against proteolytic degradation. In subjects with type 2 diabetes, after 26 weeks of treatment, oral semaglutide 10 mg and 20 mg reduced HbA1c by 1.2% and 1.4%, respectively, compared to subcutaneous semaglutide 1 mg, 1.9% [9].

Oral semaglutide 14 mg is being evaluated in the PIONEER series of clinical trials (Peptide Innovation for Early Diabetes Treatment). PIONEER 1 showed that in subjects with type 2 diabetes over 26 weeks, oral semaglutide 14 mg reduced HbA1c by 1.1% and body weight by 2.3 kg [10]. This key paper evaluation is of PIONEER 6 [1], which was primarily designed to rule out any cardiovascular safety concerns with oral semaglutide in order to obtain approval for widespread use.

2. PIONEER 6

PIONEER 6 was a non-inferiority phase 3a trial and was also placebo-controlled and randomised. To be enrolled in PIONEER 6, subjects with type 2 diabetes had to be ≥ 50 years of age with established cardiovascular disease or chronic kidney disease. Exclusion criteria included serious cardiovascular disease such as New York Heart Association class 4 heart failure, planned revascularization, myocardial infarction, stroke or hospitalization of unstable angina or transient ischaemic attack within 60 days before screening. Subjects with severe renal impairment or being treated for proliferative retinopathy or maculopathy were also excluded [1].

The 3183 enrolled subjects had a mean age of 66 years, were predominantly male (~68%) with a body mass index of 32 kg/m². The subjects had ongoing diabetes of ~15 years duration and a HbA1c of 8.2%. Subjects continued their existing anti-diabetic (metformin, ~77%; insulin, ~61%; sulfonylureas, 32%) and cardiovascular medications (anti-hypertensives, ~94%; lipid-lowering, ~85%; antiplatelet or antithrombotic, ~79%; diuretics, ~40%) into the trial [1].

Subjects were randomised to once-daily oral semaglutide (target dose, 14 mg) or placebo. To decrease gastrointestinal side effects with semaglutide, dose-escalation was used starting with 3 mg semaglutide/placebo for 4 weeks, followed by 7 mg for 4 weeks, and then 14 mg, if not limited by
adverse effects. The semaglutide or placebo was taken in the morning, in 120 ml of water, in a fasting state, and at least 30 minutes before eating, drinking, or taking other oral medications. At the end of the trial, 85% of subjects on oral semaglutide completed with 70% taking 14 mg, and the others were taking lower doses. More subjects discontinued oral semaglutide (11.6%, 184/1591) than placebo (6.5%, 104/1592) and this was predominantly due to gastrointestinal adverse effects, 6.8% vs 1.6%, respectively, including nausea, vomiting and diarrhoea [1].

During the trial, more subjects were started on SGLT2 inhibitors in the placebo than semaglutide group; 7.0% vs 3.1%. The percentages of subjects started on sulfonylureas and diuretics were also higher in the placebo than semaglutide group; sulfonylureas, 7.8% vs 3.5%; diuretics, 9.8% vs 7.1% [1].

The primary outcome as the time from randomisation to first occurrence of a major adverse cardiovascular event, a composite of death form cardiovascular or undetermined cause of death, nonfatal myocardial infarction or nonfatal stroke. At a median trial time of 15.9 months, this was non-inferior with semaglutide having occurred in 3.8% of (61/1591), compared to 4.8% on placebo (76/1592). This non-inferiority applied to the components of the primary outcome; death, 0.9% with semaglutide vs 1.9% on placebo, non-fatal myocardial infarction, 2.3% vs 1.9%, and non-fatal stroke, 0.8% vs 1.0%, respectively. There were also no differences in unstable angina and heart failure resulting in hospitalisation, between the semaglutide and placebo group [1].

HbA1c levels were lower in the semaglutide than in the placebo group; HbA1c, -1.0 vs 0.3%; respectively. Severe hypoglycaemia occurred in more subjects in the semaglutide than placebo group, 1.4% vs 0.8%, respectively. Systolic blood pressure, body weight (-4.2 vs -0.8 kg), LDL cholesterol and triglycerides were also reduced more in the semaglutide than placebo group. Mean pulse rate was increased by 4 beats/min in the semaglutide group, but not altered in the placebo group [1].

The rates of diabetic retinopathy were similar in the semaglutide and placebo groups, 7.1% vs 6.3%. There was one case of medullary thyroid cancer in a subject receiving semaglutide [1].

3. Expert Opinion

3.1 Were the benefits of semaglutide reduced by increased use of drugs in the placebo group?

In their discussion, the authors suggested that, the increased introduction of SGLT2 inhibitors in the placebo vs semaglutide group during PIONEER 6, could have lowered the cardiovascular risk in the placebo group, and lowered any potential benefit observed with oral semaglutide [1]. As the placebo group also has increased introduction of sulfonylureas and diuretics during the trial, compared to the semaglutide group, these medicines could also have improved the outcomes in the placebo group, and lowered any potential benefit with oral semaglutide.

3.2 Are surrogate endpoints relevant with semaglutide?

Some of the changes in surrogate endpoints have been shown to be similar with oral and subcutaneous semaglutide. In SUSTAIN 6 (trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes), showing cardiovascular outcome benefits with subcutaneous semaglutide, at 26 weeks, HbA1c was reduced by ~1.1%, and body weight by ~ 4 kg [6], which is like the reduction reported in PIONEER 6. The reductions in systolic blood pressure were also similar for subcutaneous and oral semaglutide. However, it is not known if these surrogate endpoints are directly relevant to reducing cardiovascular risk with semaglutide or other glitides, as the reductions in HbA1c, systolic blood pressure and body weight with the glitides are small and unlikely to underlie any benefit. Other mechanisms that may underlie the beneficial effects
of glutides include effects on lipids, especially postprandial hypertriglyceridemia, anti-inflammatory actions, and direct effects on the myocardium [11]. Small reductions in total cholesterol, LDL cholesterol and triglycerides were observed in PIONEER 6 [1], but it is unclear whether these had any benefit. No surrogate markers of inflammation have been used in the PIONEER series of clinical trials, and this may be a useful addition in future trials.

### 3.3 Gastrointestinal tolerability

In SUSTAIN 6, 9.4% of subjects discontinued subcutaneous semaglutide 1 mg due to gastrointestinal tolerability vs 1% in the placebo group [6], which is more than with oral semaglutide 14 mg vs placebo in PIONEER 6; 6.8% vs 1.6% [1], respectively. This suggests that gastrointestinal tolerability may be better with oral semaglutide 14 mg than subcutaneous semaglutide 1 mg, which favours the use of oral over subcutaneous semaglutide for this aspect.

### 3.4 Medullary thyroid cancer risk with semaglutide

As a result of liraglutide causing thyroid cancers in rats and mice, a boxed warning was added to this medication [12] and other glutides including subcutaneous semaglutide [13], despite no evidence that this occurred in humans. In SUSTAIN 6 [6], there were no medullary thyroid risk with subcutaneous semaglutide, and in PIONEER 6, there was only one case, which occurred in a subject who had pre-existing thyroid nodules and an elevated calcitonin level at baseline [1]. This suggests that the risk of medullary thyroid cancer is low or non-existent with semaglutide, and no longer requiring a boxed warning.

### 3.5 NCT03811561 and diabetic retinopathy

In the cardiovascular outcomes trial with subcutaneous semaglutide, SUSTAIN-6 [6], a higher risk of diabetic retinopathy was noted with semaglutide than placebo. Consequently, subjects with proliferative retinopathy or maculopathy resulting in active treatment were excluded from PIONEER 6, and the risk of diabetic retinopathy was similar for oral semaglutide and placebo.

A long-term trial of subcutaneous semaglutide on the risk of diabetic retinopathy is ongoing; NCT03811561. This study started in May 2019 and aims to recruit 1500 subjects with type 2 diabetes to subcutaneous semaglutide or placebo and is due to report in 2025 [14]. However, I am not sure that this trial will give us the answers we require in a reasonable timeline. In SUSTAIN 6, retinopathy complications occurred in 50/1648 subjects taking subcutaneous semaglutide and 29/1649 in the placebo group, 3.0% vs 1.8% [6]. Thus, it is questionable whether at 1500, NCT03811561 will have enough participants to pick up any small increases in retinopathy with semaglutide. Also, as NCT03811561 is being undertaken with subcutaneous semaglutide, the results will not necessarily apply to oral semaglutide.

### 3.6 Convenience and adherence with oral semaglutide

One of the main reasons given by the authors of PIONEER 6 for developing oral semaglutide was to have a preparation more convenient to use than subcutaneous semaglutide. This would alleviate the concerns that some patients have about injections and the need for physicians to alleviate these concerns and educate the patients to perform subcutaneous injections. This could allow an earlier introduction and wider use of semaglutide by patients who are needle adverse and improve adherence to semaglutide [1]. However, whether oral semaglutide is more convenient than a once-weekly subcutaneous injection of semaglutide is debatable, as oral once-daily semaglutide requires dose-escalation, is taken with 120 ml of water, in a fasting state and at least 30 minutes before eating, drinking, or taking other medication. Adherence studies have shown that a once-weekly glute
(subcutaneous exenatide) is much more likely to reach an adherence rate of ≥ 80% than once-daily subcutaneous liraglutide [15]. Thus, it should not be assumed that adherence to once-daily oral semaglutide will be higher than for once-weekly subcutaneous semaglutide, and this will need to be tested.

3.7 Why prescribe or take oral semaglutide when it has only been proven to be non-inferior?

PIioneer 6 was a short study and not designed to assess superiority [16]. Thus, to date, oral semaglutide has only been shown to be non-inferior, not superior to placebo in reducing cardiovascular risk in subjects with type 2 diabetes. Given that subcutaneous semaglutide, and other glitides (e.g. liraglutide) and SGLT-2 inhibitors (e.g. empagliflozin, canagliflozin) have already been shown to be superior to placebo in reducing cardiovascular risk, the question arises as to why oral semaglutide should presently be prescribed, or used by subjects with, type 2 diabetes. A clinical trial (NCT03914326, SOUL, A heart disease study of semaglutide in patients with type 2 diabetes) started in July 2019 to compare the effects of oral semaglutide to placebo on major adverse cardiovascular events in 9642 subjects with type 2 diabetes [17]. This trial is due for completion in July 2024, and, it seems to me, that only if oral semaglutide is found to be superior to placebo, should it be considered as an alternative to the other agents that have already been shown to be superior to placebo for the treatment of type 2 diabetes.

3.8 Will oral semaglutide be used to reduce cardiovascular risk instead of subcutaneous semaglutide?

In my opinion, there are several reasons why once-daily oral semaglutide may not replace once-weekly subcutaneous semaglutide in the treatment of type 2 diabetes. Most importantly, subcutaneous semaglutide has already been shown to be superior to placebo in reducing cardiovascular risk, whereas this has not been reported to date with oral semaglutide. Secondly, it is debatable whether subjects will find the daily protocol for taking oral semaglutide more convenient than that for the weekly subcutaneous formulation.

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