Introduction

The number of antihyperglycemic medications approved for the treatment of type 2 diabetes (T2D) has increased dramatically in recent years (1). Since the initial approval of exenatide (Byetta) by the U.S. Food and Drug Administration (FDA) in 2005 (2), agents in the glucagon-like peptide 1 (GLP-1) receptor agonist class of medications have quickly gained popularity as a treatment option for the management of hyperglycemia in T2D (3). The increase in use of GLP-1 receptor agonists is due, at least in part, to their demonstrated clinical utility in improving glycemic control and inducing weight loss in people with T2D (4).

One practical barrier to GLP-1 receptor agonist use for some individuals is the need to administer these agents via subcutaneous injection. For patients unwilling or unable to initiate a GLP-1 receptor agonist for this reason, an alternative may be available in the future—namely, an oral formulation of semaglutide that is currently in phase 3 investigation for the treatment of T2D (5). This article provides a brief discussion of once-daily oral semaglutide and the future role it may play in the management of T2D.

Mechanisms of Action

Activation of GLP-1 receptors has been shown to improve glycemic control through several mechanisms, including 1) increased glucose-dependent insulin secretion from pancreatic β-cells, 2) decreased glucagon secretion from pancreatic α-cells, and 3) delaying gastric emptying (6). GLP-1 receptor activation in the central nervous system is additionally involved in satiety signaling, thus contributing to weight loss (6). Similar to the clinical benefits expected from currently available GLP-1 receptor agonists, clinical evidence with oral semaglutide use to date demonstrates improvements in glycemic control and weight (7).

Oral semaglutide is co-formulated within a tablet with the absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate, or “SNAC” for short (7). SNAC helps facilitate semaglutide absorption in the stomach by increasing the local pH, which in turn leads to increased drug solubility and protects against proteolytic degradation (7).
Potential Advantages
If approved by the FDA, the primary advantage of oral semaglutide will be its orally available agent in its class (if approved), it will provide patients with a noninjected GLP-1 receptor agonist option. In addition, emerging clinical data suggest that this agent may have advantages in terms of glycemic efficacy and weight loss.

Results from the PIONEER 1 trial were recently reported at the American Diabetes Association’s (ADA’s) 78th Scientific Sessions (8). PIONEER 1 was a placebo-controlled trial in people with T2D. Participants were randomized to receive one of three doses of semaglutide (3, 7, or 14 mg once daily) or placebo. Participants were adults (≥18 years of age) with an A1C of 7.0–9.5%. After 26 weeks of treatment, participants receiving the 14-mg dose realized a mean decrease in A1C of 1.5% and a mean weight loss of 4.3 kg (8).

Headline results from several other trials have been reported by the manufacturer, showing superior improvements in A1C with oral semaglutide compared to empagliflozin (9) and sitagliptin (10) in the PIONEER 2 and PIONEER 3 studies, respectively. Headline results from the PIONEER 4 study additionally reported that the 14-mg dose of oral semaglutide achieved noninferiority for A1C reduction compared to 1.8 mg liraglutide, with superior weight reduction compared to liraglutide after 26 weeks of treatment (11).

Potential Disadvantages
The potential disadvantages of oral semaglutide therapy are similar to those of other agents in the GLP-1 receptor agonist class. In the largest trial completed to date with oral semaglutide, the most common adverse event associated with its use were gastrointestinal in nature (e.g., nausea and vomiting) (7). This was similarly seen in the same trial with the once-weekly injectable semaglutide formulation (7). The association of oral semaglutide with other adverse events common to the GLP-1 receptor agonist class, such as acute kidney injury and acute pancreatitis, will be investigated during phase 3 trials. Ongoing and future studies of oral semaglutide will continue to elucidate the tolerability and safety considerations of this agent.

Cost
The future cost of oral semaglutide, should it receive FDA approval, is unknown.

Commentary
The GLP-1 receptor agonist class of medications has emerged as a noteworthy advancement in the management of T2D. Guidelines from major organizations such as the ADA and the American Association of Clinical Endocrinologists/American College of Endocrinology highlight GLP-1 receptor agonists as treatment options for many patients with T2D. Although diversity does exist within the GLP-1 receptor agonist class in terms of administration frequency (twice-daily, once-daily, or once-weekly administration) and pen device functionality, all currently available agents are injectables. If approved, oral semaglutide would provide a viable choice within the class for patients who are unable or unwilling to initiate injectable therapy. Given the glycemic and weight benefits that can be realized with the use of GLP-1 receptor agonist therapy, an orally administered product would be a welcome addition to the T2D treatment toolkit.

Bottom Line
Clearly, oral semaglutide has many hurdles ahead before it attains FDA approval. That said, evidence published to date is promising. Over the past several years, the GLP-1 receptor agonist class has become a bit crowded, with one product voluntarily discontinued by the manufacturer due to a lack of market uptake (13). If approved, this oral GLP-1 receptor agonist would be a truly unique agent within the class. Emerging phase 3 data suggest that treatment with this product results in significant A1C reduction and weight loss. Only time will tell if the commercial availability of this product will become a reality.

Duality of Interest
No potential conflicts of interest relevant to this article were reported.

Author Contributions
Both authors researched data and wrote the manuscript. J.J.N. is the guarantor of this work and, as such, had full access to all of the references cited and takes responsibility for the accuracy of content.

References

