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Review Article

Orforglipron: A Promising Agent for Treatment of Obesity and Type 2 Diabetes

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Abstract

Orforglipron is a non-peptide glucagon-like receptor-1 (GLP-1R) agonist that can be orally administered once daily irrespective of food intake. Different doses of oeforglipron were evaluated in two phase 2 clinical trials including subjects with obesity and type 2 diabetes, respectively. In the obesity trial, subjects with mean baseline weight of 108.7 kg and body mass index (BMI) of 37.9 kg/m^2 had 9.4% to 14.7% of weight loss at 36 weeks compared with 2.3% loss with placebo. In the diabetes study, glycated hemoglobin (HbA1c) levels (baseline 8.1%) decreased from 1.2% to 2.1% in the orforglipron groups, 1.1% with dulaglutide (1.5 mg/week), and 0.5% with placebo at 26 weeks. In the latter trial, mean weight loss at week 26 was 3.7% to 9.6% with orforglipron, 4.0% with dulaglutide, and 2.2% with placebo. While HbA1c reduction seemed to reach a plateau at 20 weeks, weight loss continued to progress up to the end of follow-up at 36 weeks. In general, safety profile of orforglipron resembles that of GLP-1R agonists with gastrointestinal (GI) adverse effects being the most common. Yet, premature discontinuation rates were high; 19.1-21.1% across the orforglipron groups compared with 4% with dulaglutide and 2.0-5.5% with placebo. In addition, there was a pronounced increase in heart rate with the use of orforglipron; placebo-adjusted increase being 7.7-9.2 beats per minute (bpm). Overall, orforglipron is a promising oral GLP-1R agonist for treatment of obesity and type 2 diabetes. Phase 3 trials are urgently needed to clarify its long-term efficacy and safety.

Keywords: GLP-1 receptor agonists; orforglipron, semaglutide; safety; efficacy; weight; glycated hemoglobin

Introduction

Currently, the peptide semaglutide (Rybelsus) is the only oral GLP-1R approved for treatment of type 2 diabetes [1]. However, oral semaglutide is limited by strict criteria of intake that may potentially limit compliance. Thus, it must be taken in the fasting state with no more than 4 ounces (120 cc) of plain water at least 30 minutes before the first food, beverage, or other oral medications [1]. Several orally administered non-peptide GLP-1R agonists are under development for treatment of obesity and type 2 diabetes, orforglipron being the most studied so far [2,3]. Contrary to oral semaglutide, orforglipron may be taken orally once a day irrespective of food or water intake. Results of phase 2 clinical trials suggest that orforglipron may be an effective anti-obesity and anti-diabetic agent [2,3]. The main purpose of this review is to provide an appraisal on orforglipron with respect to its efficacy and safety profile.

Orforglipron for treatment of obesity:

Orforglipron was evaluated in various doses [12, 24, 36, 45 mg/d]. in a randomized phase 2 double-blind, placebo-controlled trial of 272 obese subjects (59% women, mean age 54.2 years, mean weight 108.7 kg, mean BMI 37.9 kg/m2) [2]. The starting dose and titration schedule varied between groups. Throughout the trial, education regarding healthy eating and exercise was provided to all enrolled individuals [2]. The primary and secondary endpoints of the trial were the percentage change from baseline in weight after 26 weeks and 36 weeks respectively [2]. At week 26, the mean change from baseline ranged from -8.6% to -12.6% across orforglipron groups versus -2.0% in the placebo group [2]. At week 36, corresponding changes in weight were -9.4% to -14.7% with orforglipron and was -2.3% with placebo [2]. At 36 weeks, weight reduction of ≥15% was recorded in 22 to 48% of subjects randomized to orforglipron compared with 1% in those randomized to placebo [2]. The magnitude of weight loss clearly increased from orforglipron doses 12 mg to 24 mg/d. Meanwhile, weight reduction was less pronounced with doses higher than 24 mg/d [2]. Inspection of the trajectory of weight-time curves showed that weight loss occurred early within few weeks after starting orforglipron and continued to the end of the trial at 36 weeks without evidence of a plateau effect [2].

Orforglipron for treatment of type 2 diabetes:

In another phase 2 clinical trial, orforgliflozin [3,12,24, 36 and 45 mg]. was compared with placebo and the GLP-1R agonist dulaglutide (1.5 mg subcutaneously/week) in patients with uncontrolled type 2 diabetes [3]. Patients (n=383, 41% women, mean age 58.9 years, mean BMI 35.2 kg/m^2) had mean duration of diabetes of 8 years and a baseline level of HbA1c of 8.1%. Majority of participants (86-98%) were taking metformin [3]. The primary endpoint of the study was the effect of orforglipron versus placebo on HbA1c levels from baseline to week 26.

The comparison between orforglipron and dulaglutide was a secondary end point [3]. At week 26, mean reductions in HbA1c values were -1.2% to -2.1% in the orforglipron groups, -1.1% with dulaglutide, and -0.5% with placebo [3]. All doses of orforgliflozin were superior to placebo ($P<0.0001$ for all doses) and to dulaglutide except the lowest orforgliflozin dose of 3 mg ($P\leq0.0006$) [3]. The decreases in HbA1c and fasting plasma glucose values were evident early in all patient groups (except placebo) but seemed to reach a plateau after 20 weeks [3]. Regarding weight changes, percentage weight loss ranged from -3.7% to -9.6% in the orforglipron groups, -4.0% with dulaglutide, and -2.2% with placebo after 26 weeks [3]. All orforglipron doses (except the 3 mg-dose) were superior to dulaglutide and placebo in terms of weight loss [3].

Effects of orforglipron on blood pressure and lipids

In the obesity study, at week 36, there was dose-related reduction in systolic blood pressure in the orforglipron groups (-6.9 to -10.1 mmHg) versus -1.8 mmHg in placebo [2]. Corresponding decrease in diastolic blood pressure was -1.7 to -4.0 mmHg versus -2.8 mmHg [2]. With respect to the lipid profile, there were mild reductions in plasma levels of low-density lipoprotein-cholesterol (LDL-C) (5-8% versus placebo) and triglycerides (8-15% versus placebo) [2]. The beneficial effects of orfoglipron in terms of blood pressure and lipids are most likely due to weight loss.

Safety of orforglipron

Available data suggests that tolerance to orforglipron may be suboptimal. Thus, in the obesity trial, adverse effects leading to orforglipron discontinuation occurred in 10-21% of subjects compared with 2% in the placebo group [2]. Similarly, in the diabetes study, treatment discontinuation ranged from 12 to 19% in the orforglipron groups and was much lower in the dulaglutide group (4%) and placebo group (5%) [2]. The commonest adverse effects were GI in origin similar to those of the class of GLP-1R agonists. For instance, in the obesity trial, nausea was reported by 37-58% in the orforglipron groups versus 10% in the placebo group, whereas frequency of vomiting ranged from 14 to 32% with orforglipron versus 6% with placebo [2]. In the diabetes study, vomiting occurred in 3-13% of patients among the orforglipron groups, 4% in the dulaglutide group and 1% in the placebo group [3]. Adverse effects occurred mainly during the initial dose titration phase and they were the main cause of drug discontinuation [2,3]. In general, the incidence of GI adverse effects was more common in groups of subjects starting higher orforglipron dose (3 mg/d versus 2 mg/d) with more rapid dose escalation (every 1-2 weeks versus slower escalation every 3 weeks) [2,3].

Effect of orforglipron on heart rate

Increase in heart rate, of approximately 2-6 bpm compared with placebo, was observed with use of all GLP-1 R agonists [4-7]. However, this adverse effect did not result in increase in cardiovascular events in randomized trials [5,6]. With the use of the highest oral dose of semaglutide 50 mg once daily, the placebo-adjusted increase in heart rate was 4.5 bpm in obese subjects (table 1) [7]. With respect to orforglipron, greater increase in heart rate was observed. Thus, in the obesity study, pulse increased 5.0 to 9.2 bpm with orforglipron compared with placebo [2]. Similarly, in the diabetes trial, placebo-adjusted increase in heart rate was 4.6-7.7 bmp with different doses of orforglipron [3]. Moreover, in the latter trial, 2 patients in the group receiving the smallest dose of orforglipron (3 mg/d) developed atrial fibrillation [3]. The magnitude of increase in pulse rate with orforglipron is concerning. Thus, in ongoing and future trials of orforglipron, the incidence of different types of arrhythmias should be thoroughly examined.

Orforglipron versus oral semaglutide

Recently, oral semaglutide was evaluated in higher doses of 50 mg/d in two phase 3 clinical trials of patients with obesity and type 2 diabetes [7,8]. While there are no head-to-head trials to provide direct comparison between orforglipron and semaglutide, preliminary and indirect comparison between these 2 oral GLP-1R agonists may be clinically useful. As shown in table 1, efficacy of orforglipron and oral semaglutide (50 mg/d) in terms of reduction in body weight and levels of HbA1c appear similar. However, there are important differences with respect to methods of administration and drug tolerance.

Conclusions and future needs

Orforglipron represents a new class of non-peptide GLP-1R agonists that can be taken orally once a day without food or water restrictions. Other non-peptide GLP-1R agonists, such as danuglipron, are under development [9]. Phase 2 trials lasting 26-36 weeks show that orforglipron cause an average placebo-adjusted substantial weight loss of up to 12.4% and 9.6% in subjects with obesity and type 2 diabetes, respectively [2,3]. A second phase 2 trial suggest that orforglipron is effective as antihyperglycemic agent causing an average reduction of HbA1c levels of up 1.7% [3]. The magnitude of decrease in weight and HbA1c values are close to those achieved by the highest dose of oral semaglutide (50 mg/d) shown in phase 3 clinical trials (table 1). In general, safety profile of orforglipron is comparable to that of the class of GLP-1 agonists. Yet, the incidence of GI adverse effects may be higher with orforglipron compared with other GLP-1R agonists, in part due to patterns of dose initiation and escalation. The latter observation may explain the high rates of orforgliflozin discontinuation due to adverse effects reaching up to 21% (versus 5.5% with placebo) (table 1).

	Orforglipron [2,3]	**Oral semaglutide [7,8]**
Structure	Non-peptide GLP-1R agonist	Peptide GLP-1R agonist
Method of administration	Orally once daily irrespective of food intake	Once daily in AM with no more than 120 ml of water and 30 min before any food items or other medications
Doses	3,12,24, 36, 45 mg	7,14, 25,50 mg
Phases of development	Phase 2 trials of 36 week-duration	Phase 3 trials of 52-68 week-duration.
Approval by FDA	Not yet approved	Approved for treatment of type 2 diabetes 7-14 mg doses
Percentage reduction in weight vs baseline with the highest dose in subjects with obesity	-14.7% (-12.4% vs placebo)	-15.1% (-12.7% vs placebo)
Percentage reduction in weight vs baseline with the highest dose in patients with type 2 diabetes	-9.6% (-7.4% vs placebo)	-8.5% (no placebo was used)
HbA1c reduction vs baseline with the highest dose	-2.1% (-1.7% vs placebo)	-2.0% (no placebo was used)
Adverse effects (proportions of subjects using highest dose)	Mainly GI (70.4% vs 18.2% with placebo)	Mainly GI (80% vs 46% with placebo)

Proportions of subjects who discontinued drug due to adverse effects using highest dose	19.1-21.1% vs 2.0-5.5% placebo	6-13% vs 4% placebo
Safety concerns	↑ heart rate (7.7 to 9.2 bpm vs placebo), atrial fibrillation (2 cases)	↑ heart rate (4.5 bpm vs placebo)

Abbreviations in the table: GLP-1R: glucagon-like peptide-1 receptor, FDA: Federal Drug Administration, HbA1c: glycated hemoglobin, bpm: beats per minute.

Table 1: Comparison between orforglipron and oral semaglutide

Furthermore, the increase in placebo-adjusted heart rate of 7.7 to 9.2 bpm with orforglipron appears to be more pronounced than other GLP-1R agonists. Phase 3 clinical trials are underway to clarify efficacy and safety of orforglipron in larger patient population of obesity and type 2 diabetes from different ethnic backgrounds. The changes in heart rate and any types of arrhythmias should be included as pre-specified adverse effects in these trials. More importantly, the effects of orforglipron on cardiovascular events and mortality should be evaluated in adequately powered long-term trials. In addition, direct comparison of orforglipron with oral semaglutide should be studied in the setting of double-blind trials.

Conflict of interest

The author has no conflict of interest to declare.

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