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Review Article

Orforglipron: a Step Forward Toward Simplifying Management of Obesity and Type 2 Diabetes

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Abstract:

Orforglipron is a non-peptide agonist of glucagon-like peptide-1 (GLP-1) receptor that is administered orally once-daily independent of food intake. Currently, orforglipron is under clinical development for treatment of obesity and type 2 diabetes. Three phase 3 double-blind clinical trials were recently published to evaluate efficacy and safety of orforglipron in subjects with obesity and type 2 diabetes. In individuals with obesity, mean percent weight loss at 72 weeks was -11.2% with the highest dose of orforglipron (36 mg/d) compared with -2.1% with placebo. Weight loss reached its peak after 48 weeks of intervention followed by a plateau. In patients with early type 2 diabetes, orforglipron 36 mg/d was associated with reduction of glycated hemoglobin (HbA1c) values of -1.48% versus -0.41% with placebo at 40 weeks. Discontinuation rates due to adverse effects were 5-10% with orforglipron versus 1.4-5% with placebo. Most adverse effects were gastrointestinal (GI) occurring mainly during dose escalation. Increased diabetic retinopathy with orforglipron emerged as a safety signal in one trial despite excluding patients with baseline diabetic retinopathy. In patients with type 2 diabetes, preliminary data from the ACHIEVE-3 trial suggest that orforglipron is superior to oral semaglutide in terms of glycemic control and weight loss, but drug discontinuation rates due to adverse effects are double those recorded with oral semaglutide. Overall, orforglipron is a promising GLP-1 receptor agonist characterized by its simplicity of administration. Its long-term efficacy and safety require further investigations in a broader spectrum of subjects with obesity and type 2 diabetes.

Keywords: orforglipron; obesity; diabetes; efficacy; safety; oral semaglutide

Introduction

Orforglipron (code LY3502970) is a non-peptide agonist of GLP-1 receptor under investigation in phase 3 clinical trials for treatment of obesity and type 2 diabetes [1-3]. Orforglipron helps control of type 2 diabetes by enhancing pancreatic β-cell function, increasing insulin sensitivity and lowering glucagon secretion [4]. At the cellular level, orforglipron is described as a biased agonist of GLP-1 receptor [5,6]. Being "biased" means that it enhances the G protein pathway of GLP-1 receptor that mediates GLP-1 actions while decreasing GLP-1 receptor internalization and subsequent desensitization by limiting β-arrestin recruitment at the GLP-1 receptor [5,6]. Orforglirpron is administered orally once daily with mean oral bioavailability `of 79.1% and a half-life of 47.7 h [7]. Orforglipron is metabolized by extensive hepatic oxidative metabolism. Its primary rout of elimination was via the feces (87%) with minimal urinary excretion (0.2%) [7]. Currently, the peptide semaglutide (Rybelsus) is the only oral GLP-1 receptor agonist approved for treatment of type 2 diabetes [8]. However, administration of 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 [8]. Contrary to oral semaglutide, orforglipron can be ingested irrespective of food or water intake without significant effects on its pharmacokinetics if taken after food [9]. The ATTAIN and ACHIEVE programs are a series of phase 3 clinical trials designed to evaluate the efficacy and safety of orforglipron. Three of these trials were recently published and discussed below [1-3]. The main purpose of this review is to provide an appraisal of orforglipron based mainly on results of published clinical trials.

Orforglipron evaluation in phase 3 clinical trials

Recently, orforglipron was evaluated in 3 clinical trials including the following groups of patients: those with obesity (the ATTAIN-1 trial), early type 2 diabetes (the ACHIEVE-1 trial), and obesity plus type 2 diabetes (the ATTAIN-2 trial) [1-3]. These 3 investigations were double-blind,

randomized, placebo controlled, multinational, phase 3 clinical trials (table 1).

Trial	For obesity (ATTAIN-1) [1]	For early type 2 diabetes (ACHIEVE-1) [2]	For obesity + type 2 diabetes (ATTAIN-2) [3]
Subjects' number	3127	559	1613
Subjects' demographics	45 years, 64% women, 56% Whites, 29% Asian	53 years, 48% women, 40% Hispanic, 26% Whites	57 years, 47% women, 71% Whites, 17% Asian
Baseline weight and BMI	103 kg, 37.0 kg/m^2	90 kg, 33.0 kg/m^2	101.4 kg, 35.6 kg/m^2
Baseline HbA1c	NA	8.0%	8.05%
Orforglipron doses	6 mg, 12 mg, 36 mg, placebo	3 mg, 12 mg, 36 mg, placebo	6 mg, 12 mg, 36 mg, placebo
Follow-up	72 weeks	40 weeks	72 weeks
Duration of diabetes	NA	4.4 years	6.9 years
Percent change in weight with highest orforglipron dose	-11.2% vs -2.1% placebo	-7.6% vs -1.7% placebo	-9.6% vs -2.5% placebo
Change in HbA1c with the highest orforglipron dose	NA	-1.48% vs -0.41% placebo	-1.66% vs -0.47% placebo
Discontinuation rates due to adverse effects	5-10% vs 2.6% placebo	5-8% vs 1.4% placebo	6-10% vs 5% placebo
Remarks	Diabetes excluded	Diabetic retinopathy occurred in 9.2% with the highest dose of orforglipron vs 4.3% with placebo	

Table 1: Overview of phase 3 trials of orforglipron

All trials are double-blind, placebo-controlled, multinational. Values are means. HbA1c: glycated hemoglobin, NA: non-applicable

The 3 following doses of orforglipron 6,12 and 36 mg were assessed in the ATTAIN-1 and ATTAIN-2 trial, whereas the 3 doses 3, 12, and 36 mg were evaluated in the ACHIEVE-1 trial. The starting orforglipron dose was 1 mg to be increased every 4 weeks to the next dose-level (i.e. 3 mg, 6 mg, 12 mg, 24 mg, and 36 mg, as applicable) [1-3].

Effects of orforglipron on weight loss

The main objective of the large (n=3127) ATTAIN-1 trial was to evaluate the effects of 3 once-daily doses of orforglipron (6, 12, and 36 mg) compared to placebo on weight loss in obesity without diabetes (table 1) [1]. Throughout the trial, all subjects received individualized counselling for lifestyle changes including a balanced diet combined with physical activity. After 72 weeks, the mean percent change in weight (primary end point) was -7.5% in the orforglipron 6-mg group, -8.4% in the 12-mg group, and -11.2% in the 36-mg group, compared with -2.1% in the placebo group [1]. Thus, placebo-corrected percent weight loss was -5.5%, -6.3% and -9.1% in the 6-mg, 12-mg and 36-mg orforglipron, respectively (P<0.001 for all doses vs placebo) [1]. Regarding the effects of orforglipron on body composition assessed by dual-energy x-ray absorptiometry (DXA) results obtained from a subgroup of 171 subjects, showed 73.1% of the body weight reduction was due to loss in fat mass and 26.9% was due to a loss in lean mass [1]. In the ATTAIN-2 trial, the protocol and primary end point were generally like the ATTAIN-1 trial but the latter included patients with overweight/obesity having pre-existing type 2 diabetes (table 1) [3]. In the ATTIAN-2 trial, after 72 weeks, the mean percent weight change was -5.1% in the orforglipron 6-mg group, -7.0% in the 12-mg group and -9.6% in the 36 mg group, compared with -2.5% in the placebo group. This yielded a placebo-subtracted weight loss of -2.7%, -4.5%, and -7.1%, in the 6-mg, 12-mg, and 36-mg groups, respectively (P<0.001 for all doses vs placebo) [3]. In both the ATTAIN-1 and ATTAIN-2 studies, inspection of the course of weight loss revealed that peak of weight loss was reached at 48 weeks followed by a plateau [1,3].

Effects of orforglipron on glycemic control

The main objective of the ACHIEVE-1 trial was to examine the effects of orforglipron on glycemic control in patients with early type 2 diabetes treated only by diet and exercise. After 40 weeks, mean change in HbA1c levels (the primary endpoint) were -1.24%, with the 3-mg orforglipron, -1.47% with the 12-mg, and -1.48% with the 36-mg doses versus -0.41% with placebo [2]. The placebo-subtracted differences in HbA1c values were -0.83%, -1.06% and -1.07% in the 3-mg, 12-mg, and 36-mg doses, respectively (P<0.001 versus placebo in all doses) [2]. Maximum HbA1c reduction occurred at 20 weeks followed by a plateau [2]. Therefore, contrary to the weight-reduction of efficacy of orforglipron that exhibited a dose-related effect, no such effect was clear with respect to its anti-hyperglycemic efficacy.

Effects of orforglipron on cardiovascular risk factors

Orforglipron had beneficial effects on several CV risk factors. Thus, compared with the placebo group, there was significant reduction in systolic blood pressure (-2.6 mmHg), non-high-density lipoprotein cholesterol (-3.8%), triglycerides concentrations (-12.2%), and high-density lipoprotein cholesterol (5.4%) [3]. Moreover, there was dose-related significant decrease in high-sensitivity C-reactive protein ranging from -24.9% to -41.6%, and in fasting insulin values reaching -16.4% with the highest doses of orforglipron vs placebo [3]. Furthermore, in the ATTAIN-1 trial, 83.7% of individuals receiving orforglipron who had prediabetes at randomization reverted to normoglycemia at 72 weeks, as compared with 44.6% of those receiving placebo [1]. Amelioration of these CV risk factors is most likely the result of weight loss caused by orforglipron, but direct drug effects unrelated to weight loss cannot be excluded.

Effects on quality of life

When compared to placebo, patients receiving orforglipron achieved significant improvement in several aspects of quality of life such as physical and psychosocial functioning, general health perception, and vitality [3].

Safety of orforglipron

Orforglipron was reasonably tolerated as reflected by discontinuation rates due to adverse effects of 5-10% vs 1.4-6% with placebo (table 1) [1-3]. As with other GLP-1 receptor agonists, the most common adverse effects of orforglipron were GI (nausea, vomiting, diarrhea, constipation, dyspepsia) occurring mainly during the titration phase and were generally dose-related. Another adverse effect characteristic of incretin-based agents was the increase in heart rate, presumably due to their direct action on sinoatrial node of the heart [10]. Thus, mean heart rate was increased by 2.2 to 5.3 beats per minute (bpm) in orforglipron-treated patients versus a minor change ranging from -0.9 to 0.8 bpm with placebo [1,2]. Severe hypoglycemia requiring assistance occurred in one patient on orfoglipron 6 mg/d [3]. Level 2 hypoglycemia (blood glucose < 54 mg/dl) was reported by 2.5% and 0.3% of patients randomized to orforglipron high-dose (36 mg) and placebo, respectively [3]. It should be emphasized that background insulin therapy was an exclusion criterion and therefore frequency and severity of hypoglycemia could be underestimated. While incidence of diabetic retinopathy in the orforglipron group was like the placebo group in the ATTAIN-2 trial, frequency of diabetic retinopathy was doubled with orforglipron in the ACHIEVE-1 trial being 9.2% (n=13) and 4.3% (n=6) with the highest dose of orforglipron and placebo, respectively [2]. Of note, all patients with diabetic retinopathy were excluded from the orforglipron diabetes trials, ACHIEVE-1 and ATTAIN-2 [1,3].

Orforglipron versus oral semaglutide

The only orally administered incretin-based agent is semaglutide with many restrictions as mentioned earlier and in table 2 [8]. The latter depicts the main differences between orforglipron and oral semaglutide. Recently, in a large clinical trial (n=9650), oral semaglutide (14 mg/d) was shown to significantly decrease CV events by 14% in patients with type 2 diabetes and atherosclerotic CV disease [11]. Direct comparison of orforglipron and oral semaglutide was evaluated in the ACHIEVE-3 trial [12]. The latter is a 52-week open-label trial comparing efficacy and safety of orforglipron (12-36 mg/d) with oral semaglutide (7-14 mg/d) in patients with type 2 diabetes inadequately controlled on metformin (baseline HbA1c 8.3%) [12]. Main results of the ACHIEVE-3 trial were recently published as a press release [12]. Thus, preliminary results of the ACHIEVE-3 trial showed superiority of orforglipron 32 mg versus oral semaglutide 14 mg in terms of HbA1c reduction (primary end point) being -2.2% versus -1.4% and weight loss (secondary end point) being –9.2% versus –5.3% (table 2) [12]. Meanwhile, semaglutide was better tolerated than orforglipron with discontinuation rates due to adverse effects of 9.7% and 4.9%, respectively (table 2) [12].

	Orforglipron	**Oral semaglutide**
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 [8]
Oral bioavailability	79.1% [7]	<1% [5,8]
Doses	6,12,36 mg	7,14,50 mg
Approval by FDA	Not yet approved	Approved for treatment of type 2 diabetes 7-14 mg doses [8]
*Mean reduction in weight with the highest dose at 52 weeks [12]	-9.2%	-5.3%
*Mean HbA1c reduction with the highest dose at 52 weeks [12]	-2.2%	-1.4%
*Proportions of subjects who discontinued drug due to adverse effects using highest dose [12]	9.7%	4.9%
Effect on CV events	Not evaluated	14% decrease, HR 0.86; 95% CI, 0.77 to 0.96; P=0.006) [11]

Table 2: Comparison between orforglipron and oral semaglutide in patients with type 2 diabetes

Abbreviations in the table: GLP-1R: glucagon-like peptide-1 receptor, FDA: Federal Drug Administration, HbA1c: glycated hemoglobin, bpm: beats per minute. CV: cardiovascular, MI: myocardial infarction, HR: hazard ratio.

*Based on press release of ACHIEVE-3 trial [12]

CV events: a composite of death from CV causes, nonfatal MI, or nonfatal stroke

Advantages of orforglipron

One major advantage of orforglipron lies in its ease of administration as once daily oral capsule independent of food intake, and simple storage and distribution. This simple way of intake may be convenient for subjects having needle phobia. In addition, in 3 phase 3 clinical trials, orforglipron use was associated with robust reduction in body weight and amelioration of glycemic control. Other advantages include its favorable actions on CV risk factors and on quality of life. Moreover, its cost is expected to be less than currently approved GLP-1 receptor agonists.

Limitations of orforglipron

Many important limitations regarding orforglipron still exist. First, with the longest clinical trial of orforglipron extended to only 72 weeks, the durability of its actions is unknown. Indeed, no further weight loss was observed after 48 weeks of use of orforglipron [1]. Second, the drug was not evaluated in high-risk patients such those with advanced type 2 diabetes on different anti-diabetic agents including insulin, patients with chronic kidney disease, and in the elderly. In such groups of patients, the efficacy and tolerance of orforglipron might be different than in the relatively healthy subjects enrolled in the 3 clinical trials discussed here. Third, one concerning safety signal was the doubling of rates of diabetic retinopathy with orforglipron use compared with placebo despite exclusion of patients with diabetic retinopathy [2].

Conclusions and future needs

Orforglipron is non-peptide biased agonist of GLP-1 receptor that can be orally administered once daily independent of food intake. In 3 well-designed clinical trials, orforglipron has shown consistent favorable effects on body weight, glycemic control, and CV risk factors. Therefore, the introduction of orforglipron represents a step forward in simplifying management of patients with obesity and type 2 diabetes. However, current research should focus on the sustainability of action of orforglipron, and its safety in patients with chronic kidney and liver disease. In terms of safety, current and future studies should examine the incidence of hypoglycemia, particularly when orforglipron is used in conjunction with insulin and its effects on diabetic retinopathy. Clinical trials are underway to examine the effects of orforglipron on hard outcomes such as CV events and mortality.

Conflict of interest

The authors have no conflict of interest to declare.

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