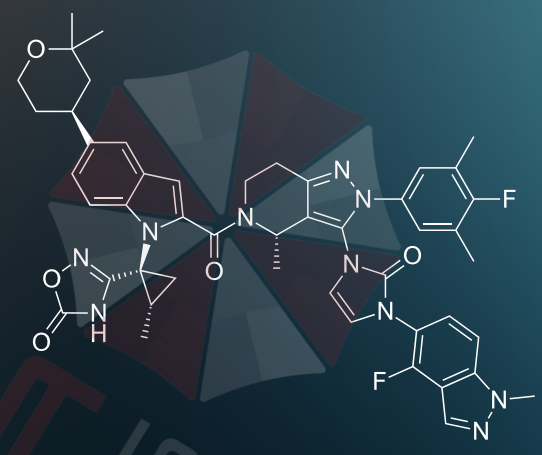

Orforglipron: An Oral Small-Molecule GLP-1 Receptor Agonist for Glycemic Control and Weight Management

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History

Orforglipron (also known as LY3502970) was developed by Chugai Pharmaceutical and 2018 licenced out by Eli Lilly. As of yet (August 2025) it is not approved for medical use anywhere. Phase I and II clinical trials have been completed and phase III trials are currently being conducted. The molecule is envisioned to be used as treatment for type-II diabetes and obesity, especially in combination with each other.

Its development by Lilly can be seen as an answer to the induction of semaglutide by Novo Nordisk in the year 2017. Its is part of a strategy to win back shares in the obesity treatment market by developing alternatives and superior treatments to semaglutide.

Synthesis

The synthesis of orforglipron has been partiallypublished published.[1]

Pharmacology

Orforglipron is, like semaglutide, an agonist of the GLP-1 receptor, which has anorectic and blood glucose lowering effects. However, in contrast to semaglutide and similar molecules, orforglipron is a small molecule type molecule, and has the advantage of being orally bioavailable.

Orforglipron has a half-life of 29 to 49 hours across the doses tested and is taken once per day in current trials.[2] Maximum plasma concentrations are achieved 8-10 hours after ingestion. Pharmacokinetics showed to be mostly independent of food and water consumption.[3]

Side effects, which appear of roughly 70% of users are mostly gastro-intestinal, they include diarrhoea, nausea, upset stomach, and constipation.[4]

Preclinical Trials

One study assesses ligand-binding characteristics at the human GLP-1R and downstream signalling events for some GLP-1 receptor agonists including orforglipron, comparing with common peptide GLP- 1 analogues such as semaglutide. Glucose-lowering pharmacodynamics and weight loss were additionally assessed in rodent models. Study details are not available.[5]

Clinical Trials

First small-scale phase 1 studies generally showed promising results for the orally active orforglipron. In a study with 51 participants, after 12 weeks HBA1c reduced by 1.5-1.8% and bodyweight reduced between 0.24 to 5.8 kg in the study group.

These results were assessed to be sufficient for further clinical development.[2]

In a phase 2 trial between September 15, 2021, and September 30, 2022, 383 participants were enrolled and randomly assigned to a group. 352 (92%) completed the study and 303 (79%) completed 26 weeks of treatment. At baseline, the mean age was 58.9 years, HbA1c was 8.1%, BMI was 35.2 kg/m2. At week 26, mean change in HbA1c with orforglipron was up to –2.10% versus –0·43% with placebo and –1.10% with dulaglutide. Change in mean bodyweight at week 26 was up to –10.1 kg with orforglipron versus –2.2 kg for placebo and –3.9 kg for dulaglutide. The incidence of treatment-emergent adverse events ranged from 61.8% to 88.9% in orforglipron-treated participants, compared with 61.8% with placebo and 56.0% with dulaglutide. The majority were gastrointestinal events (44.1% to 70.4% with orforglipron, 18.2% with placebo, and 34.0% with dulaglutide) of mild to moderate severity. Three participants receiving orforglipron and one participant receiving dulaglutide had clinically significant hypoglycemia and no participants had severe hypoglycemia. Effective dosing was found to be greater than 12 mg. This study shows that orforglipron achieved a relatively high effect on HbA1c and bodyweight compared to Dulaglutide, which is apeptidic GLP-1 inhibitor also sold by Eli Lilly.[6]

In a phase 2, randomized, double-blind trial, the authors enrolled adults with obesity, or with overweight condition plus at least one weight-related coexisting condition, and without diabetes. Participants were randomly assigned to receive orforglipron at one of four doses (12, 24, 36, or 45 mg) or placebo once daily for 36 weeks. A total of 272 participants underwent randomization. At baseline, the mean body weight was 108.7 kg, and the mean body-mass index (the weight in kilograms divided by the square of the height in meters) was 37.9. At week 26, the mean change from baseline in body weight ranged from −8.6% to −12.6% across the orforglipron dose cohorts and was −2.0% in the placebo group. At week 36, the mean change ranged from −9.4% to −14.7% with orforglipron and was −2.3% with placebo. A weight reduction of at least 10% by week 36 occurred in 46 to 75% of the participants who received orforglipron, as compared with 9% who received placebo. The use of orforglipron led to improvement in all prespecified weight-related and cardiometabolic measures. The most common adverse events reported with orforglipron were gastrointestinal events, which were mild to moderate, occurred primarily during dose escalation, and led to discontinuation of orforglipron in 10 to 17% of participants across dose cohorts. The safety profile of orforglipron was consistent with that of the GLP- 1 receptor agonist class.[7]

In another 26-week phase 2 trial of adults with type 2 diabetes treated with diet and exercise, with/without metformin, were randomized to placebo, dulaglutide 1.5 mg, or once-daily orforglipron 3, 12, 24, 36, or 45 mg. Pancreatic function significantly increased with orforglipron at doses ≥12 mg vs placebo or dulaglutide. These results suggest improved glycemic control with orforglipron vs dulaglutide may be partly explained by improved β-cell function and insulin sensitivity. Additional studies are ongoing to understand these mechanisms.[8] Further phase 2 studies have also shown promising results and safety profiles comparable to other GLP-1R agonists.[9]

A phase 3 study with 559 participants, which had its results released recently, showed that 3 mg, 12 mg and 36 mg were all similarly effective in reducing HBA1c levels and were superior to placebo. However, the effect on weight loss increased with higher doses. Patients lost 4.5 % bodyweight with 3 mg, 5.8% with 12 mg and 7.6 % with the 36 mg dose. No episodes of severe hypoglycemia were reported. Permanent discontinuation of orforglipron or placebo due to adverse events occurred in 6 % of participants receiving orforglipron and 1.4% of participants receiving placebo.[10] Preliminary results from another phase III trial also seem to confirm competitive reductions in body weight and HBA1c.

Overall, a review study concluded that Orforglipron led to a greater weight reduction in patients with type 2 diabetes or obesity compared to controls but only with a weight loss of 3.26 and 7.52 kg, respectively. The authors

concluded that preliminary evidence supports that orforglipron is efficient for inglycemic control and weight reduction in type 2 diabetes, obesity or both.[11]

As expected, orforglipron treatment was also accompanied by a reduction in many markers of cardiovascular risk, which is likely an indirect effect due to the reduction in blood glucose levels and bodyweight.[12]

Conclusion

With the current state of evidence, orforglipron is likely to be approved for the treatment of type 2 diabetes and weight management in major markets within the next years. As a small molecule with good bioavailability, it has the potential to combine efficacy with easy administration and low costs. There is a good chance, that in 10 years' time orforglipron (or another member of the same compound class) will be the standard treatment for obesity and replace current injectables from the market, depending on the price of the compound.

Orforglipron reduces blood glucose levels and bodyweight in all clinical trials conducted to far. The effects are comparable to the injectable GLP-1 receptor agonists. Adverse events in studies are mostly gastro-intestinal and of mild or moderate intensity. Severe adverse are generally not reported in clinical trials.

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