

Is retatrutide (LY3437943), a GLP-1, GIP, and glucagon receptor agonist a step forward in the treatment of diabetes and obesity?

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Key Paper Evaluation

Is retatrutide (LY3437943), a GLP-1, GIP, and glucagon receptor agonist a step forward in the treatment of diabetes and obesity?

Evaluation of Urva S, Coskun T, Loh MT et al. LY3437943, a novel triple GIP, GLP-1, and glucagon receptor agonist in people with type 2 diabetes: a phase 1b, multicentre, double-blind, placebo-controlled, randomised, multiple-ascending dose trial. Lancet 2022;400:1869-81.

1. Introduction
2. The story so far
3. Phase 1b trial with retatrutide (LY3437943)
4. Expert Opinion

Abstract

Introduction: Despite there being a wide range of medicines available for the treatment of type 2 diabetes, the high rate of mortality, suggests treatment needs to be improved. Only a few medicines have shown long-term effectiveness in obesity, and new medicines are urgently needed.

Areas covered: A multiple-ascending dose phase 1b clinical trial of a new drug retatrutide (LY3437943), which in addition to stimulating Glucagon-like peptide 1 (GLP-1) and Glucose-dependent insulinotropic polypeptide (GIP) receptors, stimulates glucagon receptors, in subjects with type 2 diabetes. Retatrutide was relatively safe and pharmacokinetics support once-weekly dosing.

Expert opinion: The role of stimulating glucagon receptors in the treatment of type 2 diabetes and/or obesity is poorly defined and needs to be clarified. Although retatrutide may be superior to the GLP-1 receptor agonist dulaglutide in reducing plasma glucose and body weight, this is not a meaningful comparison, as another GLP-1 receptor agonist (semaglutide) is more potent than dulaglutide at this and may have similar efficacy to retatrutide. Retatrutide also needs to be compared to another Eli Lilly and Company drug, the combined GLP-1 and GIP receptor agonist, tirzepatide. The safety of retatrutide needs to be determined in larger and longer trials.

Keywords diabetes, dulaglutide, GLP-1 receptors, retatrutide, obesity, semaglutide, tirzepatide

1. Introduction

This key paper evaluation is of a multiple-ascending dose phase 1b clinical trial of a new drug LY3437943 (retatrutide) that in addition to stimulating Glucagon-like peptide 1 (GLP-1) and Glucose-dependent insulinotropic polypeptide (GIP) receptors, stimulates glucagon receptors [1]. These three hormones are involved in glucose homeostasis, and consequently, manipulation may be useful in the treatment of diseases such as diabetes and obesity. The trial was in subjects with type 2 diabetes [1].

Diabetes is characterised by high levels of blood glucose, and is a major risk factor for cardiovascular, eye, kidney, and nerve disease. Diabetes affects 422 million worldwide and causes 1.5 million deaths annually [2]. Having a body mass index (BMI) over 30 kg/m² is considered obese and worldwide 650 million people are living with obesity. Obesity is a major risk factor for cardiovascular disease, diabetes, osteoarthritis, and some cancers [3]. Despite there being a wide range of medicines available for the treatment of type 2 diabetes, the high rate of mortality, suggests treatment needs to be improved. Only a few medicines have shown any effectiveness in obesity, and new medicines are urgently needed.

The present treatment of diabetes and/or obesity includes GLP-1 receptor agonists and GLP-1/GIP receptor agonists, but not glucagon receptor agonists. GLP-1 and GIP are incretins; gut hormones secreted in response to eating. They both increase meal-stimulated insulin release. GLP-1 also inhibits glucagon release in hyperglycaemic or euglycaemic states, reduces food intake and delays gastric emptying. GLP-1 receptor agonists (e.g., liraglutide, dulaglutide, and semaglutide) are used in the treatment of diabetes and obesity [4].

GIP stimulates glucagon release during fasting states and hypoglycaemic states. GIP also facilitates lipid clearance. GIP receptors are present in the appetite centres of the hypothalamus. Stimulation of these receptors decreases food intake and body weight in mice, and this effect is reduced in *CNS-mGipr* knockout mice [5]. To my knowledge, GIP receptor agonists alone are not used therapeutically. However, the dual GLP-1 and GIP receptor agonist tirzepatide has recently been introduced for the treatment of diabetes and shown to have greater benefits than semaglutide alone [6], and this may be due to the additional stimulation of GIP receptors with tirzepatide, compared to just stimulating GLP-1 receptors with semaglutide.

Glucagon, from the pancreas, stimulates its receptors (GcgR) on the liver between meals to breakdown glycogen to glucose (glycogenolysis), to activate the conversion of amino acids into glucose (gluconeogenesis), and to enhance fatty acid oxidation and lipolysis. Glucagon also stimulates insulin secretion in hyperglycaemic states, reduces appetite and increases energy expenditure, and reduces gastrointestinal motility. Recently, it has been shown in rat islet cultured cells, that glucagon can also stimulate GIP receptors and enhance GLP-1 secretion [7].

Glucagon is mainly used intravenously in the treatment of severe hypoglycaemia in unconscious insulin-using subjects. Glucagon-receptor agonists alone are not used therapeutically at present. However, it has been suggested that glucagon may add to the benefits of GLP-1 and GIP receptor agonists [1]. In the next section, the background to the clinical development of retatrutide, which is an agonist at GLP-1, GIP, and glucagon receptors, is given. Section 3 summarises the phase 1b trial of retatrutide compared to those of GLP-1 receptor agonist dulaglutide, in subjects with type 2 diabetes [1], and Section 4 is an expert opinion of the trial, and the present standing of retatrutide.

2. The story so far

Retatrutide was engineered from a GIP background and is a 39 amino acid peptide, which is resistant to cleavage by dipeptidyl peptidase IV, the enzyme that breaks down GLP-1 and GIP. It is a full agonist at the human glucagon, GLP-1, and GIP receptors with EC₅₀ values of 1.9 nM, 0.78 nM, and 0.0037 nM, respectively [8].

The effects of retatrutide have been investigated in genetically modified mice. These studies showed that retatrutide can improve glucose tolerance either through the GLP-1 or GIP receptors. In C57/B16 diet-induced obese mice, retatrutide reduced body weight, blood glucose, plasma insulin, and liver triglycerides. At 10 nmol/kg, retatrutide reduced body weight and calorie intake more than tirzepatide, and this may be due to the additional stimulation of glucagon receptors with retatrutide. In cynomolgus monkeys, retatrutide 0.05 mg/kg increased heart rate, and decreased systolic and diastolic blood pressure [8].

In a Phase 1 trial (NCT03841830) in 47 healthy volunteers, the maximal concentrations of retatrutide were obtained after 12-42 hours, and the t_{1/2} was ~6 days. Retatrutide decreased body weight and appetite. The most frequent treatment-emergent adverse events (TEAEs) were gastrointestinal including vomiting, abdominal distention, and nausea. Retatrutide increased pulse rate, which is in line with findings for dulaglutide and semaglutide [8].

3. Phase 1b trial with retatrutide (LY3437943)

A study of retatrutide in participants with type 2 diabetes mellitus (NCT04143802) was funded by Eli Lilly and Company, who had a role in all aspects of the trial [1].

3.1 Methods and results combined

To be enrolled in this Phase 1b double-blind, placebo-controlled, randomised trial, subjects had to have type 2 diabetes with an HbA1c level of 7.0-10.5%, BMI of 23-50 kg/m², without advanced complications of diabetes, and could not be taking medicines for diabetes other than metformin. The 72 subjects who were enrolled were predominantly White (82%), had a mean age of 58 years, a BMI of 32 kg/m², and HbA1c of 8.7% [1].

COVID-19 restrictions leading to withdraws disrupted the trial. Thus, although 15 were randomised to the placebo group, 8 withdrew (5 due to COVID-19 restrictions) and only 7 completed; for dulaglutide 1.5 mg, 5 were assigned, but only 2 completed. No subjects out of 9 completed with retatrutide 0.5 mg (8 COVID-19 restrictions), 1/9 with retatrutide 1.5 mg (6 COVID-19). In contrast the completions were higher with the higher doses of retatrutide; 11/11 with both retatrutide 3 mg and 3/6 mg, and 10/12 with the stepwise increased with retatrutide 3/6/9/12 mg. Treatment was once-weekly subcutaneously over 12 weeks: in the 3/6 mg group, subjects received 3 mg for 4 weeks followed by 6 mg for 8 weeks; 3/6/9/12, 3 mg for 2 weeks, then 6 mg for 2 weeks, 9 mg for 4 weeks and finally 12 mg for 4 weeks [1].

TEAEs were higher with dulaglutide 1.5 mg and the highest dose of retatrutide than with placebo. These were predominantly gastrointestinal: placebo, 33%; dulaglutide, 60%; and retatrutide 3/6/9/12 mg, 83% [1].

Dulaglutide and retatrutide 3, 3/6 and 3/6/9/12 mg reduced plasma levels of glucose, and in the oral glucose tolerance test, reduced glucose AUC_(0-2h). After 78 days, dulaglutide had reduced HbA1c by ~1.0% from baseline. Bigger reductions were observed with retatrutide; up to ~1.9%. Retatrutide also reduced glucagon AUC_(0-2h) [1].

Dulaglutide had little effect on body weight, but weight was reduced by retatrutide 3, 3/6, 3/6/9/12 mg by up to ~9 kg after 85 days. Appetite, evaluated by a visual analogue scale, showed decreases with retatrutide and dulaglutide. The higher doses of retatrutide reduced LDL-cholesterol, VLDL-cholesterol, and triglycerides, whereas dulaglutide did not. Retatrutide decreased HDL cholesterol. The high doses of retatrutide also reduced diastolic and systolic blood pressure, but increased pulse rate [1].

Pharmacokinetic data included a median time to t_{max} was 12-48 hours, and the $t_{1/2}$ was ~6 days, which makes retatrutide suitable for once-weekly dosing [1].

3.2 Discussion by authors

The authors suggest that the study shows the safety profile of retatrutide, including gastrointestinal adverse effects, is like other incretin-based medicines in the early stages of development, and that triple receptor agonism (GIP, GLP-1, and glucagon receptors) is a promising option for diabetes and obesity. The reductions in blood pressure with retatrutide are also consistent with other incretin-based medicines and are potentially beneficial. However, increases in pulse rate with retatrutide may not be beneficial, and need to be assessed over longer periods, as do all aspects of treatment with retatrutide, and ongoing trials are doing this [1] (see also Expert Opinion section).

Limitations to the study include small sample size, which were made smaller by COVID-19 restrictions. Other limitations were a restricted sample of subjects with type 2 diabetes (predominantly White), wide range of some baseline parameters e.g., BMI, which may have affected outcomes, and that the study was performed in specialised centres and may not apply generally. Tirzepatide would probably have been a better comparator than dulaglutide. The authors concluded that retatrutide should be further studied [1].

For comparison, the authors mention once-weekly GLP-1 agonists (dulaglutide, semaglutide), the combined GLP-1 and GIP receptor agonist tirzepatide, combined glucagon and GLP-1 receptor agonists (e.g., cotadutide, JNJ-64565111), and these are discussed further in the Expert Opinion section [1].

4. Expert Opinion

4.1 Clarification of why glucagon receptors agonists may be beneficial in type 2 diabetes

Glucagon has many actions (discussed in Introduction) and some of these are likely to be useful in the treatment of diabetes and obesity, but for some of them it may not be obvious how they will be beneficial e.g., increased glucose production from liver. Thus, I'm having difficulty understanding the rationale for using glucagon receptor agonists in the treatment of diabetes and obesity. Also, new mechanisms are still being discovered for glucagon such as the ability to stimulate GLP-1 receptors on cultured islets [7], and the contribution to the actions of glucagon or its receptor agonists that this makes are still to be clarified. Pre-clinical comparison of the mechanisms and actions of retatrutide, which additionally stimulates glucagon receptors, and tirzepatide that only stimulates GLP-1 and GIP receptors may be useful in elucidating the effects of glucagon receptor agonists.

In their discussion, the authors suggest the actions of glucagon, in combination with GLP-1 and GIP, "might" have novel metabolic benefits, such as increased energy expenditure and metabolic "flexibility" [1]. This does not seem to me to be a very clear rationale for developing retatrutide, and a recent review has highlighted our lack of understanding of the mechanisms of glucagon, and its role in the pathogenesis of type 2 diabetes [9]. Thus, the effects of glucagon and its receptor agonists need to be further elucidated and clarified. This should probably have occurred prior to their clinical

development. However, glucagon receptor agonists will help us to further understand the role of glucagon.

In their discussion, the authors of the phase 1b trial discuss glucagon and GLP-1 receptor agonists (e.g., cotadutide, JNJ-64565111) as drugs related to retatrutide. With the use of a dual agonist, it is not easy to differentiate, if the effects are due to glucagon receptor agonism or not. This is further complicated by the two dual agonists tested to date having different effects on fasting glucose levels. Thus, in a phase 2a short-term clinical trial of subjects who are overweight and had type 2 diabetes, cotadutide (MED10382) reduced body weight, and fasting glucose levels [10]. In contrast, in a phase 2 trial of subjects who were overweight and had type 2 diabetes, JNS-64565111 reduced body weight but not fasting blood glucose or HbA1c [11].

4.2 Limitations of phase 1b trials

It is important to remember that phase 1 trials are small and short and not to read too much into the results. The phase 1b trial with retatrutide was further limited by a high percentage of withdraws due to COVID-19. Thus, the available data/sample size was reduced by COVID-19 for the placebo and dulaglutide groups, and for the low doses of retatrutide (0.5 and 1.5 mg), making the data with these groups very limited.

As with most drugs, there were increasing adverse events with increasing doses of retatrutide. As an ascending dose protocol was used in the 12-week trial, the subjects who received the highest dose of retatrutide (12 mg), only did so for 4 weeks. Thus, the adverse events were only evaluated over four of the 12 weeks, which further limits this assessment in the short-term used in phase 1 trials.

Some of the adverse events with retatrutide are concerning e.g., decrease in HDL cholesterol and increase in pulse rate. Fortunately, these concerns will be addressed with the ongoing clinical trials with retatrutide (Section 4.4).

4.3 Which drugs should retatrutide be compared to?

In the phase 1b clinical trial with retatrutide, the GLP-1 receptor agonist dulaglutide 1.5 mg was the comparator drug. As dulaglutide is also an Eli Lilly and Company medicine, this was probably quite easy to organise and a reasonable comparison to make. However, other comparator trials need to be made with retatrutide in phase 1 or higher phase clinical trials.

For instance, in a comparator trial, two doses of another GLP receptor agonist semaglutide (0.5 and 1 mg) were shown to be superior to dulaglutide (0.75 and 1.5 mg) in reducing HbA1c and body weight in subjects with type 2 diabetes [12]. Thus, if retatrutide was going to be compared to a GLP-1 receptor agonist, it should probably have been semaglutide. Semaglutide is produced by Novo Nordisk, who may not have considered it in their interests to be involved in a comparator trial with retatrutide. Nevertheless, if a comparator trial of retatrutide with a GLP-1 receptor agonist was going to be undertaken, the more appropriate drug would have been semaglutide. As semaglutide is more potent than dulaglutide at reducing HbA1c and body weight, retatrutide may not be superior to this GLP-1 receptor agonist, and this needs to be tested.

Another appropriate comparison would probably be to tirzepatide. Prior to retatrutide, Eli Lilly and Company developed tirzepatide (LY3298176), a combined GLP-1 and GIP receptor agonist. Tirzepatide was shown to be superior to the GLP-1 receptor agonist semaglutide in subjects with type 2 diabetes inadequately controlled with metformin. Thus, in an open-label, 40-week phase 3 trial in 1879 subjects, tirzepatide (5, 10 and 15 mg) caused significantly greater reductions in HbA1c and body weight than semaglutide (1 mg). Adverse events were predominantly gastrointestinal and similar

between groups [6]. Tirzepatide has also been shown to reduce body weight in 2539 subjects living with obesity in a phase 3 placebo-controlled trial [13]. Thus, the efficacy and safety of retatrutide needs to be tested against tirzepatide in subjects living with type 2 diabetes and/or obesity. Such a trial would also help to elucidate whether adding glucagon receptor agonism with retatrutide adds anything beneficial to using dual agonism of GLP-1 and GIP receptors with tirzepatide.

It is interesting to speculate as to why Eli Lilly and Company, who have developed tirzepatide, are also developing retatrutide. Tirzepatide has already been approved by the FDA for the treatment of type 2 diabetes [14] and is also being fast tracked for approval for obesity [15]. Given that tirzepatide is expected to be a blockbuster, it is interesting to speculate as to why they are also developing retatrutide. Are they expecting retatrutide to be more beneficial than tirzepatide?

Although comparisons with semaglutide or tirzepatide and retatrutide at any phase are not presently listed on ClinicalTrials.gov., I hope they are being planned. Indirect comparisons are another possible option when more data becomes available with retatrutide.

4.4 Ongoing trials with retatrutide

Unfortunately, the inappropriate comparison with dulaglutide in subjects with type 2 diabetes is being repeated in an ongoing clinical trial. Thus, a phase 2 study of once-weekly retatrutide compared with placebo and dulaglutide in participants with type 2 diabetes (NCT04867785) is using 4 doses of retatrutide for about 43 weeks in 281 subjects who have failed to achieve glycemic control despite diet and exercise or on a stable dose of metformin [16]. Retatrutide is also being studied in people living with obesity: phase 2 study of once-weekly retatrutide compared with placebo in participants who have obesity or are overweight with weight-related comorbidities (NCT04881760) is over 18 months [17]. In the phase 1b trial of retatrutide, 6 doses were used; 0.5, 1.5, 3, 6, 9, and 12 mg, and it would be useful to know which doses are being taken forward to the phase 2 stage. However, the 4 doses of retatrutide that are being used in the phase 2 clinical trials are not specified on the clinicaltrials.gov website, which I consider to be an omission.

4.5 Is retatrutide, a GLP-1, GIP, and glucagon receptor agonist a step forward in the treatment of diabetes and obesity?

As the role of stimulating glucagon receptors in the treatment of type 2 diabetes and/or obesity is poorly defined and needs to be clarified, it is not clear what benefits, if any, that being a glucagon receptor agonist has. Although retatrutide may be superior to the GLP-1 receptor agonist dulaglutide in reducing plasma glucose and body weight, this is not a meaningful comparison, as another GLP-1 receptor agonist (semaglutide) is more potent than dulaglutide at this and may have similar efficacy to retatrutide. retatrutide also needs to be compared to another Eli Lilly and Company drug, the combined GLP-1 and GIP receptor agonist, tirzepatide. The safety of retatrutide needs to be determined in larger and longer trials. Thus, at present, we do not know whether being a GLP-1, GIP, and glucagon receptor agonist is a step forward in the treatment of diabetes and obesity.

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Declaration

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