ANALYSIS OF THE SAFETY PROFILE OF RETATRUTIDE BASED ON PHASE I AND II CLINICAL TRIALS

Analiza profilu bezpieczeństwa retatrutydu na podstawie badań klinicznych fazy I i II

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Abstract

Obesity represents an escalating global public health concern, necessitating the development and implementation of new, more effective intervention strategies. Ongoing research into novel pharmacological treatments for obesity is yielding promising results. The latest advancement in this field is retatrutide, a triple agonist targeting the receptors for glucose-dependent insulinotropic polypeptide, glucagon-like peptide-1, and glucagon. This study aims to provide a detailed analysis of the safety profile of retatrutide based on data from available phase I and II clinical trials. Retatrutide demonstrated a favorable safety profile, with gastrointestinal symptoms being the most commonly reported adverse effects. These preliminary findings are promising and warrant further investigation. Although the results are encouraging, further research is needed to elucidate the mechanisms of action of triple agonists and assess their long-term efficacy. Such studies will be crucial for guiding personalized therapeutic strategies and optimizing their clinical utility across various patient groups.

Streszczenie

Otyłość stanowi narastający problem dla zdrowia publicznego na całym świecie. Wymaga to opracowania i wdrożenia nowych, skuteczniejszych strategii interwencyjnych. Obecnie prowadzone badania nad nowymi metodami farmakoterapii w leczeniu otyłości dostarczają obiecujących wyników. Najnowszym osiągnięciem w tej dziedzinie jest retatrutyd, będący potrójnym agonistą receptorów glukozozależnego peptydu insulinotropowego, glukagonopodobnego peptydu oraz glukagonu. Praca ta ma na celu szczegółową analizę profilu bezpieczeństwa retatrutydu na podstawie dostępnych badań klinicznych fazy I oraz II. Retatrutyd wykazywał korzystny profil bezpieczeństwa, a najczęściej obserwowanymi działaniami niepożądanymi były dolegliwości ze strony układu pokarmowego. Wyniki wstępnych badań są obiecujące, co stanowi motywację do dalszego pogłębiania wiedzy na temat tego leku. Pomimo obiecujących rezultatów, niezbędne jest kontynuowanie badań w celu dokładniejszego zrozumienia mechanizmów działania trójagonistów oraz oceny ich długoterminowej skuteczności i bezpieczeństwa. Takie badania będą kluczowe do planowania spersonalizowanych strategii terapeutycznych oraz optymalizacji ich klinicznej użyteczności w różnych grupach pacjentów.

Keywords: obesity; retatrutide; multireceptor agonists

Słowa kluczowe: otyłość; retatrutyd; agoniści wieloreceptorowi

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Introduction

Obesity, according to the definition of the World Health Organization (WHO), is an excessive or abnormal accumulation of fat that adversely affects health. The assessment of obesity typically relies on the body mass index (BMI). A BMI of ≥25 kg/m² indicates overweight, while a BMI of ≥30 kg/m² indicates obesity [1].

Data published by the WHO show that in 2022, one in eight people worldwide was living with obesity. The same report indicated that approximately 2.5 billion adults – representing 43% of the global adult population – were overweight, including 890 million (16%) classified as having obesity. Data from the pediatric population are also deeply concerning. Compared to 1990, the prevalence of obesity among adolescents has quadrupled. Moreover, in 2022, over 390 million children and adolescents aged 5–19 were overweight, including 160 million with obesity [2]. In Poland, according to the Center for Public Opinion Research (CBOS), 21% of adults suffer from obesity, and 38% are overweight. In the Polish pediatric population, 12.2% of boys and 10% of girls are affected by overweight or obesity [3].

According to the World Obesity Atlas 2023, by 2035, an estimated 4 billion people will be living with overweight or obesity. As much as 51% of the adult population will be overweight, including 24% classified as obese. The most dramatic rise in obesity prevalence is expected among children and adolescents. The percentage of obese boys worldwide is projected to increase from 10% in 2020 to 20% in 2035, while that of obese girls is expected to rise from 8% to 18% [4].

Obesity is a chronic disease that does not resolve spontaneously and has a tendency to recur. If left untreated, it can lead to numerous complications, primarily cardiovascular diseases. Excess body fat contributes to the development of hypertension in 60–70% of individuals. Furthermore, approximately 80% of patients with chronic coronary syndrome have an elevated body weight. Excess adipose tissue plays a significant role in the pathogenesis of strokes – it is estimated to be responsible for 64% of ischemic strokes and 24% of hemorrhagic strokes. Furthermore, it increases the risk of venous thromboembolic disease by two- to three-fold. Excess body weight also contributes to the development of osteoarthritis, including of the spinal joints, as well as obstructive sleep apnea, stress urinary incontinence, and type 2 diabetes [5]. According to data from the Organization for Economic Co-operation and Development (OECD), overweight and obese individuals live, on average, four years shorter than those with a healthy body weight. Overweight and obesity increase the risk of death by 22–91%, which indicates their greater clinical significance than previously thought. It is estimated that in the U.S., one in six deaths is attributed to complications related to overweight or obesity [6].

According to the guidelines of the American Association of Clinical Endocrinologists and the American College of Endocrinology, three key strategies are distinguished in the treatment of obesity: lifestyle modification (including diet), pharmacological treatment, and surgical interventions. The foundation of therapy is lifestyle modification, including controlling dietary habits, increasing physical activity, and providing emotional and motivational support. This approach should be recommended to all patients with overweight or obesity. In cases where lifestyle changes fail to produce sufficient results, pharmacotherapy or surgical bariatric options are considered [7].

In recent years, many methods for treating obesity have been developed, including various pharmacological approaches. One of the promising drugs is retatrutide (RTT) – a triple agonist of glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide-1 (GLP-1), and glucagon receptors. Currently, numerous studies are underway to more precisely assess its efficacy and safety. Favorable results could pave the way for new therapeutic indications for RTT, marking a meaningful step forward in the treatment of obesity.

Aim of study

The aim of this study is to compare clinical trial data concerning the safety profile of RTT. This analysis will enable the assessment of any potential differences in the safety profile of this drug across various study conditions, which may contribute to a better understanding of its potential benefits and limitations in the context of obesity therapy.

Methodology

To accurately assess the safety profile of RTT, a detailed literature review was conducted without restrictions regarding publication date, language, or study type. Searches were carried out in databases including PubMed, IEEE Xplore, ScienceDirect, and Google Scholar using the following keywords: "retatrutide," "retatrutide and obesity," and "triple GIP, glucagon and GLP-1 receptor agonists."

Inclusion criteria encompassed studies addressing at least one of the following topics: retatrutide, obesity, or triple agonists of GIP, GLP-1, and glucagon receptors. Exclusion criteria included non-peer-reviewed publications, duplicates, and articles unrelated to the topic.

Following the preliminary screening, 122 publications were identified for further assessment. The selection process involved the removal of duplicates, detailed analysis, and the selection of the most relevant studies. Ultimately, following the application of the exclusion criteria, 25 publications were included in the analysis. The selected articles comprised various types of studies, including clinical trials, meta-analyses, and systematic reviews, providing comprehensive data on the topic under discussion.

Discussion

Current approach to obesity treatment

All patients with obesity should be advised to modify their diet and increase physical activity. In cases where such measures do not produce the desired results, pharmacological treatment should be considered. In recent years, the Food and Drug Administration (FDA) has approved several medications for obesity treatment: phentermine for short-term use, and five drugs for long-term management – orlistat, phentermine/topiramate, bupropion/

naltrexone, liraglutide, and semaglutide [8]. In a 28-week phase III trial evaluating the efficacy of the naltrexone–bupropion combination, an average weight reduction of 5.7% was observed in the treatment group, compared to 1.9% in the placebo group [8, 9]. In another phase III study evaluating the effect of liraglutide on weight reduction, a 5.7% decrease in body weight was observed in the treatment group, compared to 1.6% in the placebo group [8, 10]. Semaglutide was the first drug in phase III trials to achieve a double-digit body-weight reduction, with the STEP-1 study reporting an average decrease of 14.9% [8, 11]. The newest drug is tirzepatide, which has demonstrated the highest efficacy. In an 88-week phase III study, body weight reduction averaged 25.3% [8, 12].

The main goal of pharmacotherapy for obesity is to reduce the risk of complications and have a beneficial effect on pre-existing conditions. Currently, only semaglutide has a proven beneficial effect on cardiovascular risk, which was confirmed in the SELECT trial [8, 13].

It should be emphasized, however, that bariatric and metabolic surgery remains the most effective method for treating obesity. The guidelines from the American Association of Clinical Endocrinologists and American College of Endocrinology include a concise treatment algorithm, in which the choice of the optimal treatment depends on BMI and the presence of comorbidities [7]. In individuals with a BMI exceeding 27 kg/m^2 and obesity-related complications – such as hypertension, carbohydrate-lipid metabolism disorders, coronary artery disease, or obstructive sleep apnea – pharmacological treatment should be considered. It is also recommended for individuals with a BMI above 30 kg/m^2, regardless of the presence of comorbidities. Bariatric surgery leads to significant and sustained weight loss, as well as improvements in obesity-related conditions in the majority of patients. In an analysis involving 161,756 individuals, the mean reduction in BMI five years after surgery ranged from 12 to 17 units, with a 30-day mortality rate of 0.08% and an overall postoperative mortality rate of 0.31% [14].

Mechanism of action of retatrutide

Retatrutide is an agonist of GIP, GLP-1, and glucagon receptors. GLP-1 is an incretin hormone secreted by the gastrointestinal tract that stimulates pancreatic beta cells to produce insulin. GLP-1 receptors are found in the heart, kidneys, central nervous system, as well as in the lungs, gastrointestinal tract, and pancreas. Studies have shown that GLP-1 delays gastric emptying both after meals and during fasting. It also promotes relaxation of the stomach muscles, allowing for greater gastric distension. This results in lower postprandial blood glucose levels and has a beneficial metabolic effect on the body [15].

The second target of RTT is the GIP receptor, which is located mainly in pancreatic beta cells and in the central nervous system [16]. GIP acts synergistically with GLP-1, influences fat metabolism by promoting lipogenesis, and supports the transport of fatty acids into adipocytes. In addition, it inhibits gastric motility [17]. Both GLP-1 and GIP have incretin properties, meaning that they stimulate insulin secretion in response to the presence of glucose. When glucose levels are low, GLP-1 and GIP do not significantly affect insulin levels [18]. By delaying gastric emptying and stimulating the satiety center, both hormones indirectly promote the reduction of adipose tissue.

The third receptor targeted by RTT is the glucagon receptor. These receptors are located in the liver, kidneys, adrenal glands, spleen, and the central nervous system. Glucagon is a peptide hormone that plays a key role in regulating blood glucose levels. It is secreted by pancreatic alpha cells in response to decreased blood glucose. This hormone stimulates processes such as lipolysis, gluconeogenesis, and glycogenolysis, which leads to an increase in blood glucose levels. It has an effect opposite to that of insulin. Furthermore, glucagon affects other tissues, increasing protein catabolism and releasing amino acids into the bloodstream [19]. By acting on these three receptors, RTT mimics the body's natural hormones, which enables the regulation of blood glucose levels and exerts a beneficial metabolic effect [20].

In vitro and preclinical studies on retatrutide

Retatrutide, also known as LY3437943, is a novel pharmacological agent developed by Eli Lilly for the treatment of obesity. Unlike earlier generations of drugs with similar indications, it acts on three receptors: GIP, GLP-1, and glucagon. The first stage in evaluating this novel compound involved *in vitro* studies of its mechanism of action. Results published in 2019 showed that RTT effectively stimulates glucose synthesis in hepatocytes in a manner similar to the endogenous action of glucagon in human cell models. Moreover, similar to the natural hormones GIP and GLP-1, RTT effectively initiates lipolysis in adipocytes [21, 22].

In 2018, the first studies evaluating the effects of RTT in rodents were published, confirming its triple agonistic activity toward the GIP, GLP-1, and glucagon receptors [21, 23, 24]. In one of these studies, the effects of RTT on body weight, body composition, energy metabolism, and fatty liver were also analyzed. The results showed that administration of the drug led to weight loss and reduced caloric intake, with these effects being dose-dependent (the maximum change in body weight during the study reached up to 59.7%). The mice primarily lost adipose tissue, with minimal impact on muscle mass. For example, in the group receiving 30 mg of RTT, fat mass decreased by 86.8%, while lean body mass was reduced by 31.1% compared to baseline values. A reduction in blood glucose and insulin levels was also observed, which suggests a potential improvement in glycemic control and insulin sensitivity [25].

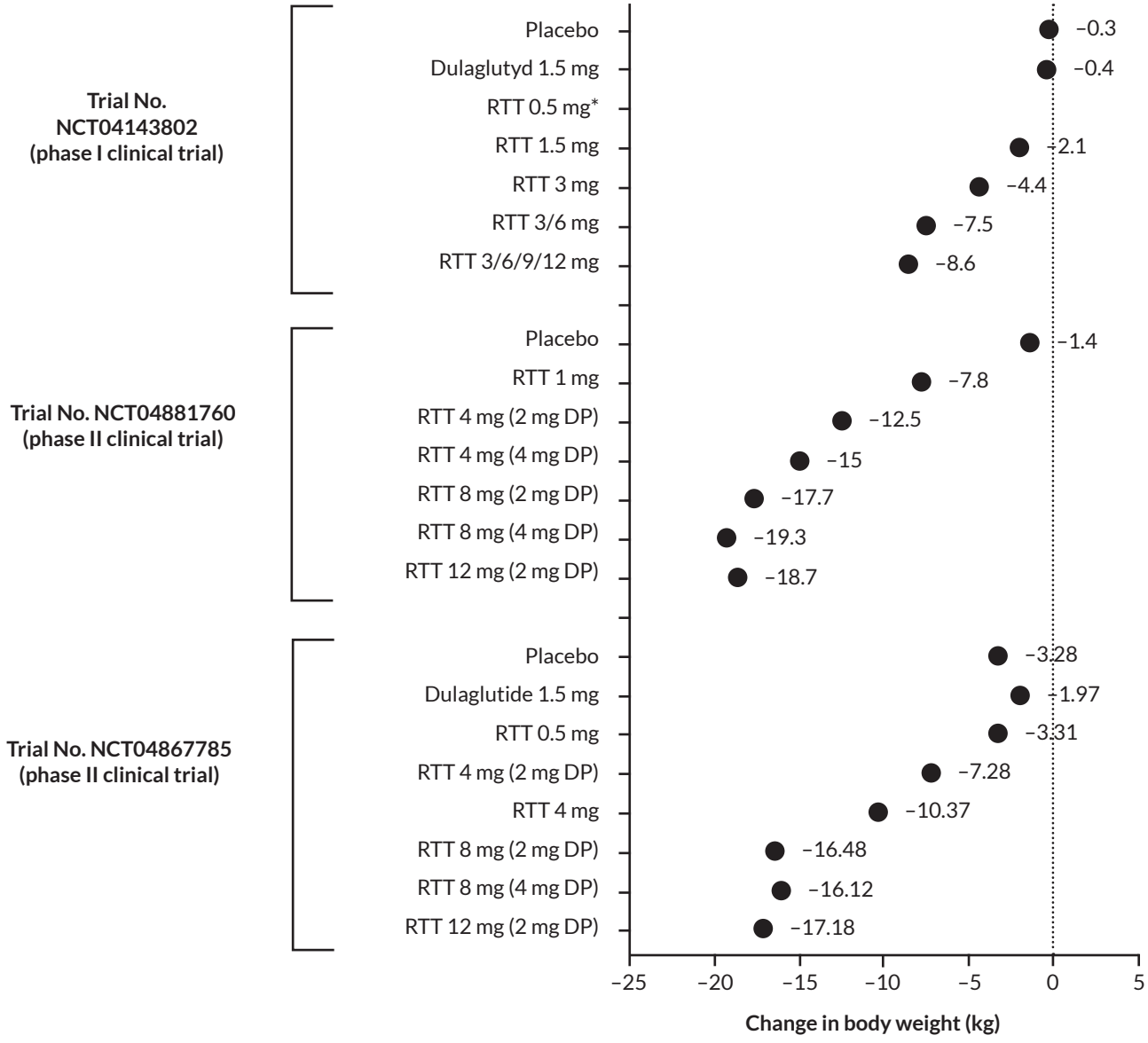
In 2022, a study was conducted comparing the efficacy of tirzepatide and RTT in reducing body weight in obese mice. Tirzepatide, the first dual agonist of GLP-1 and GIP receptors, resulted in a body weight reduction of 21.2%. In contrast, RTT, administered daily at a dose of 10 nmol/kg, led to a body weight loss of 36.9%, which was accompanied by a significant decrease in calorie intake [21].

Phase I clinical trial NCT04143802

Following the promising results of *in vitro* and animal studies, a phase I clinical trial (NCT04143802) was ini-

tiated [26]. The aim was to evaluate the adverse effects of LY3437943 in patients with type 2 diabetes. As part of the study protocol, blood analyses were performed to assess the pharmacokinetic and pharmacodynamic properties of the study drug, as well as its effects on the body. Participants in the study were randomly assigned to groups receiving subcutaneous injections of LY3437943, dulaglutide, or placebo to enable comparison of the study drug's effects with those of the control therapies. The study included patients with diabetes lasting at least 3 months, glycated hemoglobin (HbA1c) ≥7.0% and ≤10.5%, treated with diet or metformin, with stable body weight for three months, and a BMI between 23 kg/m² and 50 kg/m². The study involved 72 volunteers who were administered placebo, dulaglutide, or RTT. Only 42 patients completed the study, largely due to the COVID-19 pandemic. Among the 72 participants, half (37 individuals) were women, with a mean age of 58 years and a mean BMI of 32 kg/m². Phase I clinical trial results showed that RTT significantly reduced daily blood glucose levels by −4.4 mmol/L and HbA1c levels by −1.9% in the three patient groups receiving the highest doses of the drug. Additionally, systolic blood pressure demonstrated an overall decreasing trend from baseline in the groups receiving LY3437943 (RTT), with a reduction of 12 mmHg. A slight downward trend was also observed in diastolic blood pressure, which decreased by approximately 2 mmHg. Additionally, a dose-dependent reduction in body weight was recorded, reaching up to −8.6 kg. The most significant weight loss occurred in the group receiving escalating doses of the drug (3 mg → 6 mg → 9 mg → 12 mg). The dose-dependent weight reduction is illustrated in Figure 1.

Treatment-related adverse events (AEs) were reported in 33 (63%) of 52 participants receiving LY3437943, three (60%) of five participants receiving dulaglutide 1.5 mg, and eight (53%) of 15 participants in the placebo



ID – initial dose; RTT – retatrutide
*Due to COVID-19 pandemic-related constraints, no participants were able to complete the study.

Figure 1. Body weight changes by study drug and dosage in clinical trials NCT04143802, NCT04881760, and NCT04867785

Table 1. Safety profile based on phase I and II clinical trials

Trial	Subgroup	At least 1 AE *n* (%)	Serious AE *n* (%)	AE leading to drug discontinuation *n* (%)	Death *n* (%)
Subgroup	Placebo (*n* = 45)	28 (62)	3 (7)	2 (4)	0
	RTT 0.5 mg (*n* = 47)	26 (55)	3 (6)	1 (2)	0
	RTT 4 mg (2 mg DP) (*n* = 23)	13 (57)	1 (4)	0	0
	RTT 4 mg (*n* = 24)	19 (79)	2 (8)	1 (4)	0
	RTT 8 mg (2 mg DP) (*n* = 26)	19 (73)	2 (8)	3 (12)	0
	RTT 8 mg (4 mg DP) (*n* = 24)	17 (71)	1 (4)	4 (17)	0
	RTT 12 mg (2 mg DP) (*n* = 46)	35 (75)	2 (4)	7 (15)	0
	Dulaglutide 1.5 mg (*n* = 46)	31 (67)	1 (2)	1 (2)	0
	Entire group (*n* = 281)	188 (67)	15 (5)	19 (7)	0
NCT04881760 [20]	Placebo (*n* = 70)	49 (70)	3 (4)	0	0
	RTT 1 mg (n = 69)	58 (84)	3 (4)	5 (7)	0
	RTT 4 mg (2 mg DP) (*n* = 33)	24 (73)	0	2 (6)	0
	RTT 4 mg (4 mg DP) (*n* = 33)	28 (85)	2 (6)	3 (9)	1 (3)
	RTT 8 mg (2 mg DP) (*n* = 35)	28 (80)	1 (3)	5 (14)	0
	RTT 8 mg (4 mg DP) (*n* = 35)	33 (94)	2 (6)	2 (6)	0
	RTT 12 mg (2 mg DP) (*n* = 62)	57 (92)	2 (3)	10 (16)	0
	Entire group (*n* = 337)	277 (82)	13 (4)	27 (8)	1 (<1)
NCT04143802 [19]	Placebo (*n* = 15)	8 (53)	1 (7)	0	1 (7)
	Dulaglutide 1.5 mg (*n* = 5)	3 (60)	1 (20)	0	0
	RTT 0.5 mg (*n* = 9)	3 (33)	1 (11)	1 (11)	0
	RTT 1,5 mg (*n* = 9)	5 (56)	1 (11)	2 (22)	0
	RTT 3 mg (*n* = 11)	5 (46)	0	0	0
	RTT 3/6 mg (*n* = 11)	9 (82)	0	0	0
	RTT 3/6/9/12 mg (*n* = 12)	11 (92)	0	1 (9)	0
	Entire group (*n* = 72)	44 (61)	5 (7)	4 (6)	1 (1)

ID – initial dose; RTT – retatrutide; AE – adverse event

group. Additionally, 23 (44%) of 52 participants treated with LY3437943 experienced adverse events considered related to the study drug. The incidence of these AEs increased with higher drug doses.

The most frequently reported gastrointestinal adverse events were diarrhea and nausea. They occurred in nine (33%) placebo-treated participants, 12 (60%) dulaglutide-treated participants, and 24 (46%) LY3437943-treated patients. Throughout the study, four participants (6%) discontinued treatment due to adverse events, two of which were considered related to the treatment. Four participants reported six serious AEs, none of which were assessed as being associated with the study drug. One death occurred in a participant receiving placebo, resulting from a car accident.

Phase II clinical trial NCT04881760

Following the completion of phase I studies, two separate phase II trials were conducted [27, 28]. The primary objective of the NCT04881760 trial was to evaluate the percentage change in body weight from baseline in adults after 24 and 48 weeks of treatment [28]. The study was a randomized, double-blind, placebo-controlled trial that included adults with a BMI of at least 30 kg/m² or a BMI between 27 kg/m² and 30 kg/m² who had at least one comorbidity related to excess body weight. The participants were randomly assigned to seven groups in a 2:1:1:1:1:2:2 ratio, each receiving different doses of subcutaneously administered RTT (1 mg, 4 mg [with an initial dose of 2 mg], 4 mg [with an initial dose of 4 mg], 8 mg [with an initial dose of 2 mg], 8 mg [with an initial dose of 4 mg], 12 mg [with an initial dose of 2 mg]) or placebo. The drug was administered once weekly for 48 weeks. Secondary endpoints included change in body weight after 48 weeks and the percentage of participants who achieved a weight reduction of at least 5%, at least 10%, or at least 15%. An equally important aspect was the evaluation of the drug's safety profile. The study included 338 patients, 52% of whom were men. The mean body weight was 107.7 kg, and the mean BMI was 37.3 kg/m², with as many as 30% having a BMI >40 kg/m². Body weight changes observed during the study, stratified by administered dose, are shown in Figure 1. Throughout the trial, AEs during the treatment period were reported in 70% of participants in the placebo group and in 73–94% of those receiving RTT. The highest incidence of these events was observed in the groups receiving 8 mg and 12 mg doses. Treatment discontinuation due to adverse events occurred in 6% to 16% of participants receiving RTT, whereas no placebo-group participants discontinued treatment for this reason. The most frequently reported adverse events were gastrointestinal symptoms, including nausea, diarrhea, vomiting, and constipation, which occurred more commonly in RTT-treated patients

Table 2. The most common AEs in phase I and II clinical trials

Test	Subgroup	Nausea *n* (%)	Diarrhea *n* (%)	Constipation *n* (%)	COVID-19 *n* (%)	Vomiting *n* (%)
NCT04867785 [21]	Placebo (*n* = 45)	2 (4)	2 (4)	1 (2)	3 (7)	1 (2)
	RTT 0,5 mg (*n* = 47)	2 (4)	1 (2)	3 (6)	5 (11)	1 (2)
	RTT 4 mg (2 mg DP) (*n* = 23)	2 (9)	2 (9)	2 (9)	3 (13)	1 (4)
	RTT 4 mg (*n* = 24)	6 (25)	6 (25)	4 (17)	1 (4)	0
	RTT 8 mg (2 mg DP) (*n* = 26)	7 (27)	5 (19)	3 (12)	1 (4)	2 (8)
	RTT 8 mg (4 mg DP) (*n* = 24)	10 (42)	7 (29)	2 (8)	1 (4)	4 (17)
	RTT 12 mg (2 mg DP) (*n* = 46)	9 (20)	7 (15)	5 (11)	2 (4)	5 (11)
	Dulaglutide 1,5 mg (*n* = 46)	8 (17)	4 (9)	3 (7)	4 (9)	4 (9)
	Entire group (*n* = 281)	46 (16)	34 (12)	23 (8)	20 (7)	18 (6)
NCT04881760 [20]	Placebo (*n* = 70)	8 (11)	8 (11)	2 (3)	14 (20)	1 (1)
	RTT 1 mg (*n* = 69)	10 (14)	6 (9)	5 (7)	13 (19)	2 (3)
	RTT 4 mg (2 mg DP) (*n* = 33)	6 (18)	4 (12)	5 (15)	4 (12)	4 (12)
	RTT 4 mg (4 mg DP) (*n* = 33)	12 (36)	4 (12)	2 (6)	6 (18)	4 (12)
	RTT 8 mg (2 mg DP) (*n* = 35)	6 (17)	7 (20)	4 (11)	6 (17)	2 (6)
	RTT 8 mg (4 mg DP) (*n* = 35)	21 (60)	7 (20)	4 (11)	12 (34)	9 (26)
	RTT 12 mg (2 mg DP) (*n* = 62)	28 (45)	9 (15)	10 (16)	15 (24)	12 (19)
	Entire group (*n* = 337)	91 (27)	45 (13)	32 (9)	70 (21)	34 (10)
NCT04143802 [19]	Placebo (*n* = 15)	2 (13)	2 (13)	1 (7)	No data	0
	Dulaglutide 1,5 mg (*n* = 5)	2 (20)	3 (60)	0	No data	1 (20)
	RTT 0,5 mg (*n* = 9)	0	1 (11)	0	No data	0
	RTT 1,5 mg (*n* = 9)	0	3 (33)	1 (11)	No data	1 (11)
	RTT 3 mg (*n* = 11)	1 (9)	1 (9)	1 (9)	No data	0
	RTT 3/6 mg (*n* = 11)	4 (36)	2 (18)	1 (9)	No data	0
	RTT 3/6/9/12 mg (*n* = 12)	6 (50)	6 (50)	1 (8)	No data	3 (25)
	Entire group (*n* = 72)	15 (2)	17 (2)	5 (7)	No data	5 (7)

ID – initial dose; RTT – retatrutide

compared to placebo. These adverse events primarily occurred during the dose-escalation phase, were typically mild to moderate in severity, and showed increased frequency in higher-dose groups. Participants who started therapy at a lower initial dose (2 mg compared to 4 mg) reported less severe symptoms. These events were also the most common reason for treatment discontinuation. A detailed analysis of the safety profile is presented in Table 1.

Phase II clinical trial NCT04867785

Between May 13, 2021, and June 13, 2022, a phase II clinical trial (NCT04867785) was conducted in the United States to evaluate the efficacy and safety of RTT at various doses in patients with type 2 diabetes [27]. It was a randomized, double-blind, placebo-controlled study conducted across 42 sites. A total of 281 participants took part, with a mean age of 56.2 years and an average diabetes duration of 8.1 years. Of the study group, 56% (156 individuals) were women, and 84% (235 individuals) were Caucasian. All participants were required to implement lifestyle modifications, including increased physical activity. Eligibility criteria included a diagnosis of type 2 diabetes with an HbA1c level ranging from 7.0% to 10.5%. Prior to the study, participants were managed exclusively with diet and exercise or a stable dose of metformin for at least three months before screening. They were then randomized into eight groups (in a 2:2:2:1:1:1:1:2 ratio) to receive weekly subcutaneous injections of either placebo, 1.5 mg dulaglutide, or RTT at maintenance doses: 0.5 mg; 4 mg (with an initial dose of 2 mg); 4 mg (without dose escalation); 8 mg (with an initial dose of 2 mg); 8 mg (with an initial dose of 4 mg); or 12 mg (with an initial dose of 2 mg). The study results demonstrated that weight loss was significantly greater in groups receiving RTT doses ≥4 mg compared to both the 1.5 mg dulaglutide group and the placebo group. Detailed data on changes in body weight are presented in Figure 1. During the study, at least one treatment-related adverse event was reported by 68% of RTT-treated patients (129 of 190), with incidence increasing dose-dependently – from 55% (26 of 47) in the 0.5 mg group to 79% (19 of 24) in the 4 mg group. In the placebo group, it was 62% [28 out of 45], and in the dulaglutide group – 67% [31 out of 46]. The most commonly reported adverse effects related to RTT involved the gastrointestinal system and occurred more frequently in the RTT groups – from 13% to 50% in the RTT group, compared with 13% in the placebo group and 35% in the dulaglutide group. Gastrointestinal adverse effects were more frequent with higher doses of RTT, particularly in groups where the initial doses were 4 mg compared with 2 mg. Most of them were mild to moderate in severity. A to-

Table 3. Details regarding the methodology, inclusion criteria, and endpoints of the phase III TRIUMPH clinical trials

	TRIUMPH-1 [22]	TRIUMPH-2 [23]	TRIUMPH-3 [24]	TRIUMPH-4 [25]
Placebo	+	+	+	+
Double-blind design	+	+	+	+
Randomization	+	+	+	+
Number of participants	2100	100	1800	405
Inclusion criteria (all must be met)	• ≥18 yo • BMI ≥30.0 kg/m², or ≥27.0 kg/m² with ≥1 of the following conditions: hypertension, dyslipidemia, OSA, or CVD • ≥1 unsuccessful dietary effort to reduce body weight	• ≥18 yo • BMI ≥27.0 kg/m² • T2DM • Stable treatment of T2DM for at least 90 days • ≥1 unsuccessful dietary effort to reduce body weight	• ≥18 yo • BMI ≥35.0 kg/m² • CVD with ≥1 of the following: prior MI, prior ischemic or hemorrhagic stroke, or symptomatic PAD • ≥1 unsuccessful dietary effort to reduce body weight	• ≥18 yo • BMI ≥27.0 kg/m² • ≥1 unsuccessful dietary effort to reduce body weight • Others*
Aim of study	Evaluation of the efficacy and safety of RTT in participants with obesity or overweight, including subgroups with OA and OSA	Evaluation of the efficacy and safety of RTT in participants with T2DM and obesity or overweight, including the subgroup of participants with OSA	Evaluation of the efficacy and safety of once-weekly RTT administration in participants with obesity and CVD	Evaluation of the safety and efficacy of weekly RTT administration in participants with obesity or overweight and OA
Study duration	89 weeks	89 weeks	113 weeks	77 weeks
Intervention model	Equal allocation between placebo and RTT			
Endpoints	• Percentage change in BW relative to baseline • Change from baseline in WOMAC score for the OA subgroup • Change from baseline in AHI for the OSA subgroup	• Percentage change in BW relative to baseline • Change from baseline in AHI for the OSA subgroup	• Percentage change in BW relative to baselinea	• Percentage change in BW relative to baseline • Change from baseline in WOMAC score

OA – osteoarthritis; OSA – obstructive sleep apnea; WOMAC – Western Ontario and McMaster Universities Osteoarthritis Index; AHI – Apnea-Hypopnea Index; T2DM – type 2 diabetes mellitus; CVD – cardiovascular disease; BW – body weight; MI – myocardial infarction; PAD – peripheral artery disease

* Others:
- Knee pain lasting for >12 weeks prior to screening and knee pain present for >15 days during the past month.
- Knee X-ray showing moderate radiographic changes (grade 2 or 3 on the Kellgren-Lawrence scale).
- Currently meets the American College of Rheumatology criteria (clinical and radiological) for OA.

tal of 16 out of 190 participants (8%) discontinued treatment due to adverse effects, most commonly gastrointestinal (3% of participants). A detailed analysis of the safety profile is presented in Table 1 and Table 2.

Phase III clinical trials: TRIUMPH

After obtaining promising results in phase II studies, four phase III trials were initiated within the TRIUMPH program [29–32]. These studies include patients with class III obesity and – depending on the protocol – individuals with cardiovascular diseases, obstructive sleep apnea, or degenerative joint diseases. The trials aim to assess the efficacy and safety of RTT when administered once weekly. All studies are conducted in a randomized, double-blind, placebo-controlled design. They commenced in May 2023, with completion scheduled for February 2026. Details regarding the methodology, inclusion criteria, and endpoints are presented in Table 3.

Limitations

The present work, being a literature review, aimed to collect, assess, and synthesize available research on a specific topic; however, it does not meet the criteria of a systematic literature review. This type of analysis entails certain limitations that should be taken into account. First, subjectivity in material selection may influence the presented perspective on the issue. Moreover, the lack of original empirical data means that the conclusions are based solely on the interpretation of available publications. The complexity of the topic, combined with the difficulties of synthesizing findings from varied sources, may further limit the ability to draw definitive

conclusions. Therefore, it is important to recognize that a literature review is a valuable but not the only tool in the research process, and it should be complemented by other methods of scientific analysis.

Conclusions

Retatrutide is a novel drug that represents a promising therapeutic option for the treatment of obesity. This review summarizes the available data on its efficacy and safety, based on findings from phase I and II clinical trials. RTT has been shown to not only effectively regulate glycemia but also to induce significant weight loss, while maintaining a relatively favorable safety profile. However, attention should be paid to adverse effects, particularly those involving the gastrointestinal system. Most of them were mild to moderate in severity. Nevertheless, data on the long-term safety of the drug are lacking. Although the results obtained to date are promising, further comparative studies involving larger patient groups are necessary to confirm the therapeutic potential and safety of this novel triple agonist of GLP-1, GIP, and glucagon receptors.

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