REVIEW ARTICLE

Navigating retatrutide safety: comprehensive insights from systematic review and meta-analysis

Vikas Maharshi[1], Shruti Singh[1], Pramod Kumar Manjhi[1], Sunil Kumar Singh[1], Alok Kumar[1], Rajesh Kumar[1]

[1]Department of Pharmacology, All India Institute of Medical Sciences, Patna, Bihar, India.

Corresponding Author: Rajesh Kumar **Email:** drrajeshm@aiimspatna.org

Received: 5 December 2024 **Revised:** 23 February 2025 **Accepted:** 29 March 2025 **Available online:** January 2026
DOI: 10.55131/jphd/2026/240123

ABSTRACT

Retatrutide, a triple agonist (GIP, GLP-1, glucagon receptors), has shown promise in glycaemic control and weight loss, but its safety profile has not been studied in earlier studies. This study aims to systematically evaluate the safety profile of retatrutide by analyzing the incidence and risk of treatment-emergent adverse events. Through a comprehensive review of existing literature, the study seeks to quantify the relative risk of adverse effects, to inform clinical decision-making and future research directions. A systematic literature review following PRISMA 2020 guidelines was conducted across PubMed, Google Scholar, and Science Direct, focusing on studies investigating retatrutide's safety, and we excluded other studies (systematic reviews, narrative reviews, meta-analyses, etc.). Adverse event data, including treatment-emergent adverse events, were pooled and analysed for frequency and risk estimation. A total of 1,331 studies were initially identified, and after applying stringent inclusion and exclusion criteria, four studies were included in this Meta-analysis. We found that retatrutide significantly increased the incidence of adverse events compared to placebo (RR 1.87; 1.25, 2.80; p=0.003), with gastrointestinal disturbances (Nausea, decreased appetite, vomiting, constipation, etc.) being the most common. No significant difference in serious adverse events was observed (RR 0.81; 0.36, 1.83; p=0.61). Adverse events of special interest, such as hypersensitivity and pancreatitis, were notably higher in the retatrutide group (RR 2.94; 1.85, 4.69; p<0.00001). Retatrutide is effective for glycemic control and weight loss, but it increases the incidence of treatment-emergent adverse events, especially gastrointestinal issues, hypersensitivity, and pancreatitis. While serious adverse events were not significantly higher, careful patient selection, dose titration, and monitoring are crucial for patients with GI disorders, hypersensitivity, hepatic disease, cardiac disease etc. Clinicians should assess risks, particularly in vulnerable patients. Future research should explore the long-term safety of retatrutide and compare it with other therapies to refine treatment strategies and improve clinical decision-making.

Keywords:
retatrutide, triple agonist, safety, adverse events

Citation:
Vikas Maharshi, Shruti Singh, Pramod Kumar Manjhi, Sunil Kumar Singh, Alok Kumar, Rajesh Kumar. Navigating retatrutide safety: comprehensive insights from systematic review and meta-analysis. J Public Hlth Dev. 2026;24(1):318-338 (https://doi.org/10.55131/jphd/2026/240123)

INTRODUCTION

Type 2 diabetes is a chronic, multifactorial condition often linked to obesity, a key factor in insulin resistance and other metabolic disorders. The disease is characterized by insulin resistance in peripheral tissues and the pancreatic endocrine failure to produce insulin, resulting in persistent hyperglycaemia. This interplay contributes significantly to the disease's progression and maintenance.[1-3] Effective diabetes management emphasizes glucose and bodyweight reduction, ideally with dual-action treatments. Current guidelines advocate for a primary target of 5–15% weight loss, as achieving over 10–15% can significantly alter disease progression, reduce cardiovascular risk, and potentially induce remission of type 2 diabetes. This weight reduction serves as a crucial strategy in comprehensive diabetes care. [1,2] Newer glucose-lowering agents, such as GLP-1 receptor agonists, help many patients achieve glycaemic targets while also reducing cardiovascular risk and providing significant weight reduction. These agents represent a multifaceted approach to diabetes management, addressing both glycaemic control and associated comorbidities.[1]

Weight management is a crucial aspect of treating type 2 diabetes in individuals who are overweight and obese. Reducing body weight can enhance insulin sensitivity and address both metabolic and non-metabolic cardiovascular risk factors.[4] Treatments like incretins and sodium-glucose cotransporter-2 inhibitors, which facilitate weight loss, are preferred in such scenarios. However, these pharmacological agents often result in modest weight loss, necessitating more effective treatments.[5] Metabolic surgery offers significant benefits for individuals with type 2 diabetes and a high BMI (≥35 kg/m²), frequently resulting in diabetes remission and improvement in obesity-related comorbidities.[6] While bariatric surgery provides strong evidence of substantial weight loss benefits on metabolic disorders, its application is limited by high short-term costs, low patient acceptance, and scalability challenges. Consequently, despite its efficacy in reducing the public health impact of obesity, bariatric surgery is not widely implemented, underscoring the need for more accessible and effective weight management strategies in diabetes care.[4]

Glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are crucial incretin hormones for nutrient metabolism regulation. GLP-1 receptor agonists decrease food intake, delay gastric emptying, enhance meal-stimulated insulin secretion, and inhibit glucagon release under both hyperglycaemic and euglycemic conditions.[7] Both short- and long-acting GLP-1 receptor agonists improve glycaemic control and reduce body weight in type 2 diabetes.[4,5] GIP also promotes insulin secretion in response to meals and aids lipid clearance but differs from GLP-1 by stimulating glucagon secretion during fasting and hypoglycaemia.[7-9] Tirzepatide, a unimolecular agonist targeting both GIP and GLP-1 receptors, approved by the US FDA, results in significant reductions in glycated haemoglobin A1c (HbA1c) and body weight, alongside improvements in cardiovascular risk factors, including blood pressure and lipid profile.[10] These effects are notably greater compared to those achieved with the selective GLP-1 receptor agonist semaglutide 1 mg, suggesting enhanced efficacy from dual-incretin receptor targeting.[10] The safety profiles of tirzepatide and semaglutide are similar, with gastrointestinal adverse events being the most common.[10]

Glucagon, a peptide hormone secreted by pancreatic α cells, is crucial for glucose metabolism, primarily by increasing hepatic glucose output between meals.[11] It also contributes to body weight reduction by reducing appetite, enhancing

energy expenditure, decreasing gastrointestinal motility, promoting hepatic fatty acid oxidation and lipolysis, and stimulating insulin secretion during hyperglycaemia.[11-14] Postprandially, glucagon in conjunction with GLP-1 and GIP, regulates amino acid metabolism and ensures proper nutrient substrate disposal.[11,15] The combined effects of glucagon, GIP, and GLP-1 may provide novel metabolic benefits, including increased energy expenditure and enhanced metabolic flexibility. This synergy suggests a potential new therapeutic strategy for managing type 2 diabetes in individuals who are overweight or obese.

Retatrutide (LY3437943; Eli Lilly) is a once-weekly peptide with 39 amino acids, conjugated to a C20 fatty diacid, and acts as an agonist at GIP, GLP-1, and glucagon receptors. It shows reduced potency at human GCG and GLP-1 receptors (0.3 and 0.4 times, respectively) but increased potency at the GIP receptor (8.9 times).[16] Preclinical studies indicate that retatrutide reduces food intake and enhances energy expenditure, likely due to its glucagon receptor agonism.[16] It exhibits dose-proportional pharmacokinetics with a half-life of approximately 6 days, supporting weekly dosing.[17] Retatrutide was associated with a significant reduction in body weight and improvement of metabolic markers in patients who are overweight, obese and/or T2D patients.[18,19]

Retatrutide's safety profile presents notable concerns relative to other incretin-based therapies such as Semaglutide and Tirzepatide, primarily due to its enhanced glucagon receptor activity. While GLP-1 receptor agonists like Semaglutide and dual GLP-1/GIP receptor agonists like Tirzepatide are associated with gastrointestinal adverse effects (e.g., nausea, vomiting, diarrhea), the addition of glucagon receptor agonism in Retatrutide may exacerbate these effects through its role in increasing gastric motility inhibition and energy expenditure. Clinical trial data suggest a higher incidence of gastrointestinal-related adverse events, including severe nausea and vomiting, with Retatrutide compared to other agents, potentially limiting patient adherence. Moreover, glucagon receptor activation can increase hepatic glucose output, which, while beneficial for metabolic flexibility, may elevate the risk of hyperglycemia in certain populations. Additionally, glucagon-mediated lipolysis and hepatic fat oxidation raise concerns regarding potential adverse hepatic effects, such as transient elevations in liver enzymes.

Retatrutide demonstrates significant metabolic benefits, including enhanced glycemic control and substantial weight loss, its triplet agonism raises safety concerns that require further investigation. The increased incidence of gastrointestinal adverse events, potential risks of hyperglycemia, and hepatic effects necessitate comprehensive long-term safety evaluations. Regulatory agencies must carefully assess these risks before approving widespread clinical use. Existing research lacks extensive real-world safety data and long-term adverse event profiling. This study aims to bridge this gap by systematically evaluating Retatrutide's safety profile, focusing on adverse event incidence, severity, and clinical implications in comparison to established incretin-based therapies.

METHODS

Protocol of the present systematic review and meta-analysis was entered in the International Prospective Register of Systematic Reviews (PROSERO) and subsequently published and registered (registration ID: CRD42024580545). Results of the present systematic review and meta-analysis have been reported according to the 'Preferred Reporting Items for Systematic

Review and Meta-Analysis (PRISMA) 2020 guidelines'.

Search Strategy and Study Selection

Search strings were formulated and executed across the electronic databases PubMed, Google Scholar, and Science Direct, covering publications from inception to September 30, 2024. The studies were searched using the keywords "Retatrutide," "Triple Agonist," "LY3437943," "Retatrutide and Adverse Events," and "Retatrutide and Safety Profile."

Inclusion and Exclusion Criteria

All studies published as full-text articles in indexed journals, encompassing all levels of evidence and investigating retatrutide globally from inception, were included. Only articles published in English with accessible abstracts were considered, without any restrictions on the publication date. We excluded systematic reviews, meta-analyses, review articles, conference abstracts, commentaries, correspondences, expert opinions, letters to the editor, animal studies, unpublished reports, and book chapters.

Data Extraction and Analysis

Two authors (R.K. and V.M.) independently screened the data from the selected studies by examining the abstracts. Non-eligible studies were excluded based on duplicates and predefined exclusion criteria, after which the full texts of the remaining articles were assessed for eligibility. To minimize bias, the authors reviewed and discussed all selected manuscripts, references, and excluded articles. Any disagreements were resolved by consensus; with input from a third author (S.S.) when necessary. Finally, a manual search was conducted through the reference lists of the included papers to identify any potentially missed studies.

For each study included in the present review, the following data were extracted: author name, Year of study, Study Site, Study Design, Clinical trial number, Inclusion Criteria, Sample Size, Characteristics of participants, Intervention group (N), Control group (N), and Safety Measure Findings.

For each study, the following data were also extracted: adverse events during treatment or treatment emergent adverse events, serious adverse event, death during treatment period, adverse events leading to discontinuation of retatrutide or placebo, adverse events of special interest, treatment-emergent adverse events occurring in ≥5% of total participants, treatment-emergent adverse events occurring in < 5% of total participants frequency.

Data Synthesis

The quality and characteristics of the studies were systematically tabulated and descriptively analysed.

Ethics

Since this study is a systematic review utilizing scientific articles available on public platforms and does not involve any patient-identifiable information, an ethics committee review and approval were not necessary.

Assessment of risk of bias

Risk of bias was assessed using Cochrane's risk of bias tool 2 (RoB2) beta version 9' by three independent review authors (SS, RK and VM). Any disagreement was resolved through discussion and/or involving a fourth author (PKM), if required.

Assessment of heterogeneity

Heterogeneity was assessed using the Cochrane 'Q' statistics and the I^2 test. For simplicity of interpretation, I^2 values of <30, 30–59, 60–74, ≥75 were considered to indicate 'low', 'moderate', 'substantial' and 'considerable' heterogeneity, respectively, among the included studies.

Statistical analysis

Data were entered into a Microsoft Excel sheet. Relevant summary measures of safety of intervention were analysed using odds ratio and risk ratio. Meta-analysis was performed in the Cochrane's software 'Review Manager (RevMan) version 5.4.1'. Meta-analysis was performed using a random effects model. A p-value of <0.05 was considered statistically significant.

RESULTS

Literature Search

Based on the eligibility criteria, a total of 1,331 studies were initially identified from three distinct databases. After the removal of 286 duplicate entries, 1,045 articles remained available for preliminary review. Subsequent to the application of stringent inclusion and exclusion criteria, 503 articles were retained for further evaluation. Ultimately, following a comprehensive assessment of titles, abstracts, and full-text articles, 4 studies were selected for inclusion in this systematic review and meta-analysis. The PRISMA flow diagram provides a detailed visualization of the study selection process (Figure 1).

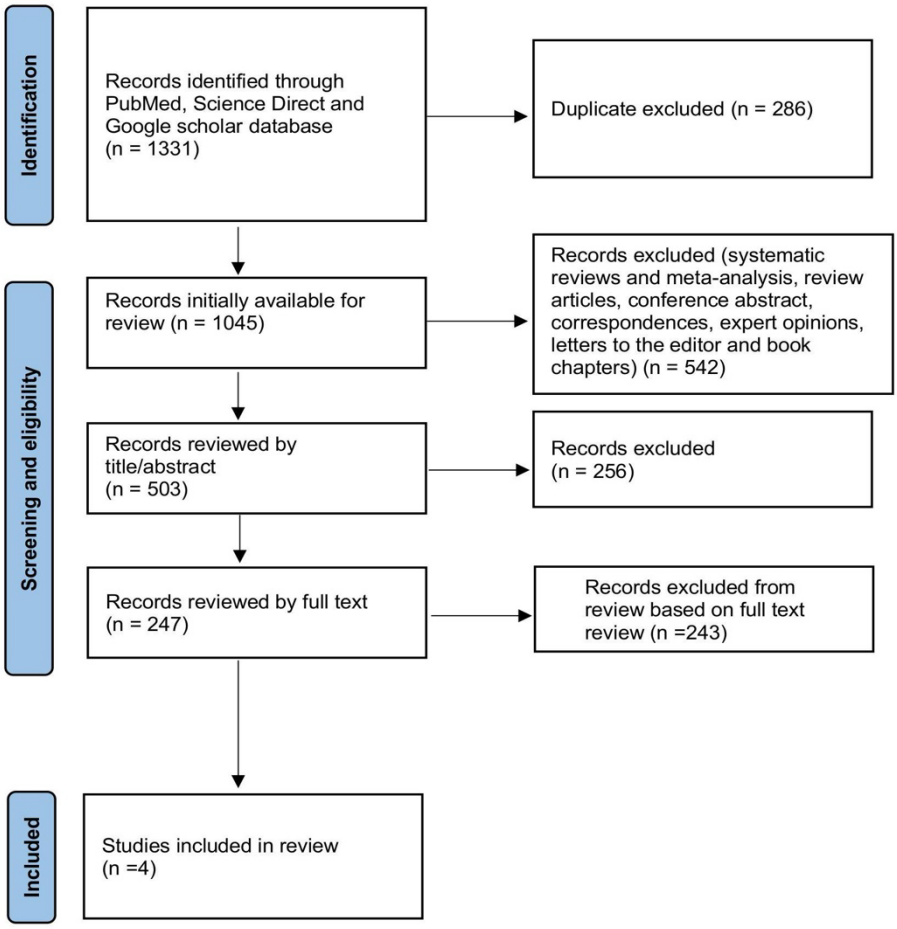

Figure 1. PRISMA flow chart of study selection for systematic review

Characteristics of studies

There are four studies included in this systematic review and meta-analysis. Characteristics of included studies are provided in Table 1.

Table 1. Characteristics of studies

Author/ Year/ Study Site	Study Design/ Clinical trial No.	Inclusion Criteria	Sample Size/ Characteristics	Intervention group (N)	Control group (N)	Safety Measure Finding
Ania M. Jastreboff et al. 2023 [19] USA	NCT04881760 Phase 2, multicentre, randomized, double-blind, placebo-controlled trial 48-week treatment period, followed by a 4-week safety follow-up period	Persons who were 18 to 75 years of age; BMI of 30 to 50 or BMI of 27 to less than 30 in addition to at least one weight-related condition	338 participants 51.8%: Men	Subcutaneously once weekly for 48 weeks Retatrutide 1 mg =69, Retatrutide 4 mg with an initial dose of 2 mg=33, Retatrutide 4 mg with an initial dose of 4 mg=34, Retatrutide 8 mg with an initial dose of 2 mg=35, Retatrutide 8 mg with an initial dose of 4 mg=35,	Subcutaneously once weekly for 48 weeks Placebo= 70	1. Adverse events during the treatment period were reported in 70% of the participants in the placebo group and in 73 to 94% of the participants in the retatrutide groups, with the highest incidence in the 8-mg and 12-mg groups. 2. Most frequently reported adverse events were gastrointestinal (nausea, diarrhea, vomiting, and constipation) and occurred more frequently with retatrutide than with placebo. 3. Gastrointestinal adverse events in the retatrutide groups occurred primarily during dose escalation, were predominantly mild to moderate in severity, were more frequent in higher-dose groups, were partially mitigated by the use of a lower starting dose 4. Discontinuation of retatrutide or placebo due to adverse events occurred in 6 to 16% of the participants who received retatrutide and in none of the participants who received placebo.

Author/ Year/ Study Site	Study Design/ Clinical trial No.	Inclusion Criteria	Sample Size/ Characteristics	Intervention group (N)	Control group (N)	Safety Measure Finding
				Retatrutide 12 mg with an initial dose of 2 mg=62		5. Fifteen serious adverse events occurred in 13 participants, with similar frequencies in the retatrutide group and the placebo group (4% in both Groups). 6. One death due to drowning occurred in a participant who received retatrutide and was assessed by the site investigator as not related to retatrutide. 7. No cases of clinically significant hypoglycaemia medullary thyroid cancer, or C-cell hyperplasia were reported. 8. Transient increases in alanine aminotransferase (ALT) levels to more than 3 times the upper limit of the normal range occurred in 1% of the participants who received retatrutide. 9. Increases in amylase and lipase levels were asymptomatic with the exception of one serious adverse event(acute pancreatitis). 10. The heart rate increased in a dose-dependent manner with retatrutide up to 24 weeks and then declined thereafter. 11. Reported cardiac arrhythmias were mild to moderate in severity with the exception of one severe adverse event (prolonged

Author/ Year/ Study Site	Study Design/ Clinical trial No.	Inclusion Criteria	Sample Size/ Characteristics	Intervention group (N)	Control group (N)	Safety Measure Finding
						QT syndrome) in a participant treated with ondansetron 12. Cutaneous hyperesthesia and skin sensitivity adverse events were reported in 7% of the participants who received retatrutide and 1% of those who received placebo. None of these events were severe or serious or were associated with overt skin findings, and none led to discontinuation of retatrutide or placebo.
Julio Rosenstock et al. 2023 [20] USA (42 Centre)	NCT04867785 Randomised, double-blind, double-dummy, placebo controlled and active comparator-controlled, parallel-group, phase 2 study 3-week screening and 36-week treatment	Persons who were Age of 18–75 year with type 2 diabetes; HbA1c of 7·0–10·5%; BMI of 25–50 kg/m2 Eligible participants were treated with diet and exercise alone or with a stable dose of metformin (≥1000 mg once daily) for at least 3	281 participants Mean age 56·2 years [SD 9·7]; Mean duration of diabetes 8·1 years [7·0]; 156 [56%]female; 235 [84%] White)	Once-weekly injections/ single-dose pen Retatrutide 0.5mg=47 Retatrutide 4 mg escalation group (starting dose 2 mg) =23 Retatrutide4mg (no escalation) =24 Retatrutide 8mg slow escalation	Once-weekly injections/ single-dose pen Placebo=45	1. At least one treatment-emergent adverse event was reported in 129 (68%) of 190 participants in the retatrutide groups (from 26 [55%] of 47 in the 0·5 mg group to 19 [79%] of 24 in the 4 mg group) versus 28 (62%) of 45 in the placebo group and 31 (67%) of 46 in the 1·5 mg dulaglutide group. 2. Most frequently reported treatment-emergent adverse events with retatrutide treatment were gastrointestinal, most commonly nausea, diarrhoea, vomiting, and constipation. 3. Gastrointestinal treatment-emergent adverse events occurred in more participants in the retatrutide groups (from six [13%] of 47 in the 0·5 mg group to 12 [50%] of 24 in the 8 mg fast

Author/ Year/ Study Site	Study Design/ Clinical trial No.	Inclusion Criteria	Sample Size/ Characteristics	Intervention group (N)	Control group (N)	Safety Measure Finding
	period, followed by a 4-week safety follow-up period	months before the screening visit They had stable bodyweight (±5 kg for 3 months before randomisation) and a BMI of 25–50 kg/m² at the first screening visit.		(from 2 mg to 4 mg to 8 mg) =26 Retatrutide 8mg fast dose escalation (from 4 mg to 8 mg) =24 Retatrutide 12mg (from 2 mg to 4 mg to 8 mg to 12 mg) =46 Dulaglutide 1.5mg group=46		escalation group) than in those in the placebo group (six [13%] of 45) and 1·5 mg dulaglutide group (16 [35%] of 46). 4. Gastrointestinal treatment-emergent adverse events were generally more common with higher retatrutide doses and occurred more frequently in the 4 mg rather than the 2 mg starting dose groups. Most gastrointestinal treatment-emergent adverse events were mild to moderate in severity. 5. Overall, 16 (8%) of 190 participants in the retatrutide groups discontinued treatment due to an adverse event, most frequently gastrointestinal adverse events (six [3%] participants). 6. Overall, 20 serious adverse events occurred in 15 (5%) of 281 participants (13 events in 11 [6%] of 190 in the retatrutide groups, six events in three [7%] of 45 participants in the placebo group, and one event in one [2%] of 46 participants in the 1·5 mg dulaglutide 1·5 mg group). 7. In the retatrutide groups, three serious adverse events were attributed to study drug by the site investigator: one case of

Author/ Year/ Study Site	Study Design/ Clinical trial No.	Inclusion Criteria	Sample Size/ Characteristics	Intervention group (N)	Control group (N)	Safety Measure Finding
						cholecystitis (in the 8 mg fast escalation group), one case of acute pancreatitis (in the 8 mg slow escalation group, 7 days after the initial and only dose), and one case of diabetic and starvation ketoacidosis (in the 12 mg escalation group). One other case of adjudication-confirmed pancreatitis was reported in the retatrutide 0·5 mg group and not attributed to study drug by the site investigator. 8. No participants died during the study. 9. Moderate hypoglycaemia (glucose <54 mg/dL [3·0 mmol/L]) was reported in one participant in each of the retatrutide 4 mg, 8 mg slow escalation, and 12 mg escalation groups. 10. In terms of adverse events of special interest, No severe or serious events of hypoglycaemia occurred, and no events of severe persistent hyperglycaemia, thyroid malignancies, or C-cell hyperplasia were reported. 11. Mean alanine aminotransferase and aspartate aminotransferase generally decreased from baseline with retatrutide treatment, with little change in bilirubin.

Author/ Year/ Study Site	Study Design/ Clinical trial No.	Inclusion Criteria	Sample Size/ Characteristics	Intervention group (N)	Control group (N)	Safety Measure Finding
Shweta_Urva et al. 2022 [18] USA (4 centre)	NCT04143802 Phase 1b, double-blind, placebo-controlled, randomised, multiple-ascending dose study 12-week treatment period	Adults aged 20-70 years with type 2 diabetes for at least 3 months, HbA_{1c} 7·0-10·5%, body-mass index of 23-50 kg/m^2, and stable bodyweight (<5% change in previous 3 months)	72 participants 37 (51%) were female, mean age was 58·4 (SD 7·4) years, and mean BMI 32·1 (5·1) kg/m^2.	Once-weekly subcutaneous injections Dulaglutide 1·5 mg=5 LY3437943(0.5mg) =9 LY3437943(1·5 mg) =9 LY3437943(3mg) =11 LY3437943(3/6 mg) =11 LY3437943(3/6/9/12 mg) =12.	Once-weekly subcutaneous injections Placebo = 15	1. Treatment-emergent adverse events (TEAEs) were reported by 33 (63%) of the 52 participants who received LY3437943, three (60%) of the five participants who received dulaglutide 1·5 mg, and eight (54%) of the 15 participants who received placebo. 2. Gastrointestinal TEAEs were reported in nine (33%) participants who received placebo, 12 (60%) participants who received dulaglutide 1·5 mg, and 24 (46%) participants who received LY3437943. Diarrhoea and nausea were the most frequently reported gastrointestinal TEAEs. 3. Within the LY3437943-treated groups, higher proportions of participants in the 3/6/9/12 mg group reported gastrointestinal-related TEAEs (including diarrhoea, nausea, abdominal distention, eructation, dyspepsia, vomiting, and soft faeces) compared with the lower LY3437943 dose groups. 4. Most gastrointestinal-related TEAEs were mild or moderate and resolved within approximately 10 days of onset, despite continuing study treatment exposure.

Author/ Year/ Study Site	Study Design/ Clinical trial No.	Inclusion Criteria	Sample Size/ Characteristics	Intervention group (N)	Control group (N)	Safety Measure Finding
						5. 23(44%) of the 52 participants who received LY3437943 reported TEAEs that were considered related to study treatment, as determined by the investigator. The proportion of participants with TEAEs that were considered related to study treatment increased with increasing dose of LY3437943. However, with the exception of the LY3437943 3/6/9/12 mg group and the 3/6 mg group, the proportion of participants with TEAEs in the LY3437943-treated groups was similar to or less than that observed in the placebo and dulaglutide 1·5 mg groups. 6. Four (6%) participants discontinued because of a TEAE. Of these TEAEs, two were considered related to study drug: one treatment-related adverse event of diarrhoea in the LY3437943 1·5 mg group and one treatment-related adverse event of nausea after the 6 mg LY3437943 dose at week 4 in the 3/6/9/12 mg group. 7. Six serious adverse events were reported in four participants, none of which were related to study drug.

Author/ Year/ Study Site	Study Design/ Clinical trial No.	Inclusion Criteria	Sample Size/ Characteristics	Intervention group (N)	Control group (N)	Safety Measure Finding
						8. One death occurred in a placebo-treated participant due to a motor vehicle accident. 9. In terms of adverse events of special interest, there were no reported TEAEs relating to pancreatitis, major adverse cardiovascular events, severe persistent hypoglycaemia, thyroid malignancies, C-cell hyperplasia, cardiovascular events, hypersensitivity reactions, injection-site reactions, hepatobiliary disorders, severe gastrointestinal events, or acute renal events during the study. 10. Overall, 15 (18%) participants reported decreased appetite, with the highest incidence observed in the 3/6/9/12 mg group. 11. Mean alanine aminotransferase and aspartate aminotransferase concentrations decreased from baseline to end of treatment in all groups except for the dulaglutide 1·5 mg group.

Author/ Year/ Study Site	Study Design/ Clinical trial No.	Inclusion Criteria	Sample Size/ Characteristics	Intervention group (N)	Control group (N)	Safety Measure Finding
Coskun et al. 2022 [17] Singapore	NCT03841630 First-in-human, Phase 1, single-site, investigator- and participant-blinded, randomized, placebo-controlled, single ascending dose study	Healthy males or females of ages between 21 and 65 years; BMI 19-40 kg/m2; HbA1c level of <6.5% at screening	47 healthy participants	Single dose subcutaneously (SC) LY3437943(0.1mg) =6 LY3437943(0.3 mg) =6 LY3437943(1 mg) =6 LY3437943(3 mg) =6 LY3437943(4.5 mg) =6 LY3437943(6 mg) =5	Single dose subcutaneously Placebo = 10	1. Treatment-emergent adverse events (TEAEs) were reported in 44 (97.8%) of the participants, of whom 23 (51.1%) reported TEAEs related to study treatment. 2. The proportion of participants with TEAEs related to study treatment increased from 16.7% to 100% with increasing doses of LY, compared with 30% in the placebo arm. 3. Most frequently reported study treatment-related TEAEs were gastrointestinal disorders including vomiting, abdominal distention, and nausea. 4. Most TEAEs were mild, with 6 moderate TEAEs (vomiting and nausea) reported by 2 participants in the 4.5 mg LY dose group. 5. No deaths or other serious adverse events occurred during this study. 6. Transient increases in concentration of pancreatic enzymes were reported in the first 2 weeks after dosing in participants receiving LY doses R3 mg, with levels returning to baseline within 4–6 weeks.

Overall adverse events

All four included studies reported the incidence of adverse events. Overall number of adverse events was significantly higher in participants receiving retatrutide than those receiving placebo with an effect estimate of 1.87 (OR 1.87; 95% CI 1.25, 2.80; p=0.003). Heterogeneity was acceptable with an I^2 value of 0% [Figure 2a].

Serious adverse events

Coskun T, et al. 2022[16] did not find any serious adverse events among the participants. Pooled results from the remaining three studies showed no significant difference in the risk of SAEs between retatrutide and placebo groups, with an overall effect estimate of 0.81 (RR 0.81; 95% CI 0.36, 1.83; p=0.61). Heterogeneity was low with an I^2 value of 0% [Figure 2b].

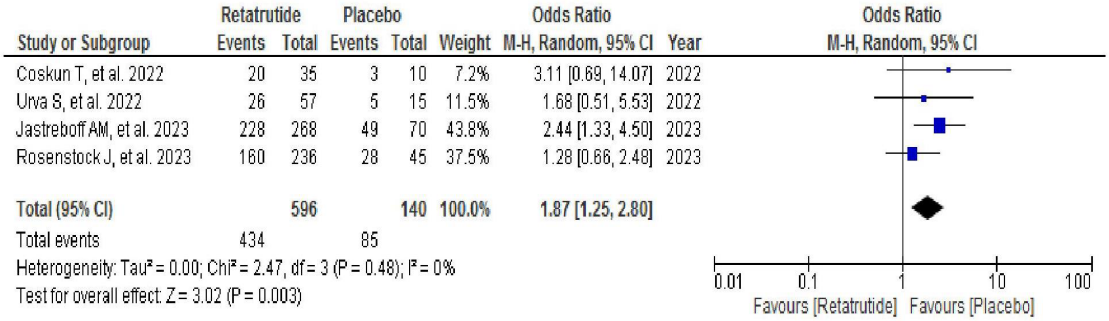

Figure 2a: Overall Adverse Events

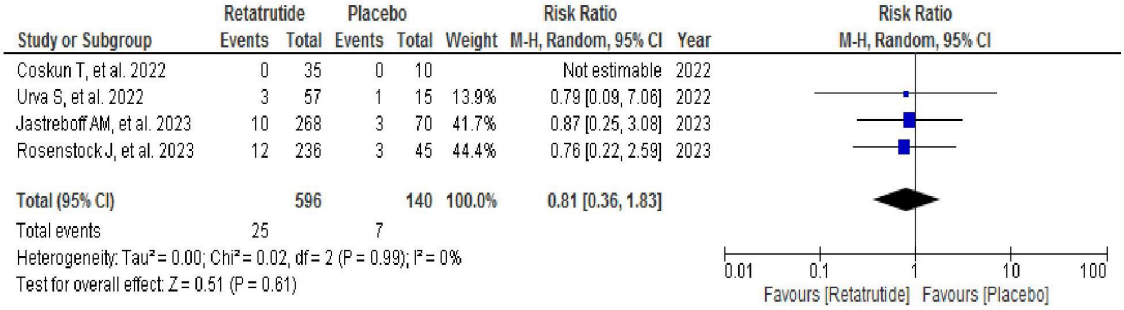

Figure 2b: Serious Adverse Events

Discontinuation of intervention due to adverse events

The study by Coskun T, et al. 2022[16] did not have any discontinuations due to adverse events. Pooled results from the other three studies show no significant difference in the risk of intervention discontinuation due to adverse events between retatrutide and placebo groups (RR 2.77; 95% CI 0.73, 10.55; p= 0.14). Heterogeneity was low with an I^2 value of 15% [Figure 3a].

Adverse events of special interest

Two of the included studies, *viz* Rosenstock J, et al. 2023[19], and Jastreboff AM, et al. 2023[18] reported adverse events of special interest including

hypersensitivity, hyperaesthesia, cardiac events including conduction abnormalities, development of anti-drug antibodies, hepato-biliary disorders, GI disturbances, hypoglycaemia, pancreatitis, injection site reaction, renal impairment, depression and/or suicidal ideation. Overall effect estimate shows statistically significant difference in the risk of developing adverse events of special interest between the retatrutide and placebo (RR 2.94; 95% CI 1.85, 4.69; p= 0.00001). Heterogeneity was low with an I^2 value of 0% [Figure 3b].

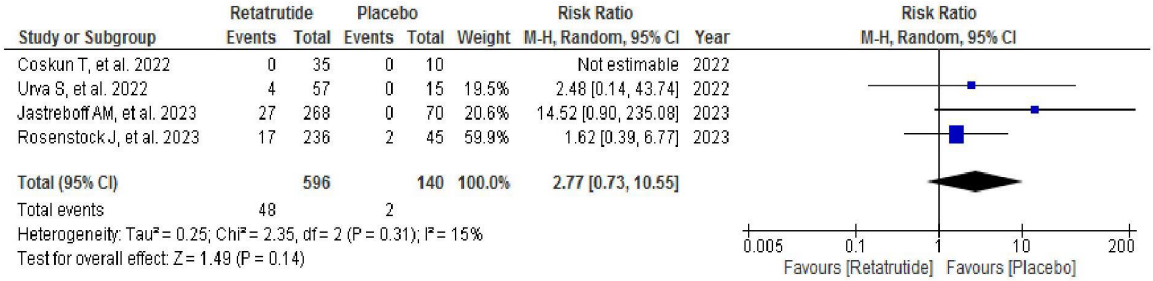

Figure 3a: Intervention discontinuations due to AEs

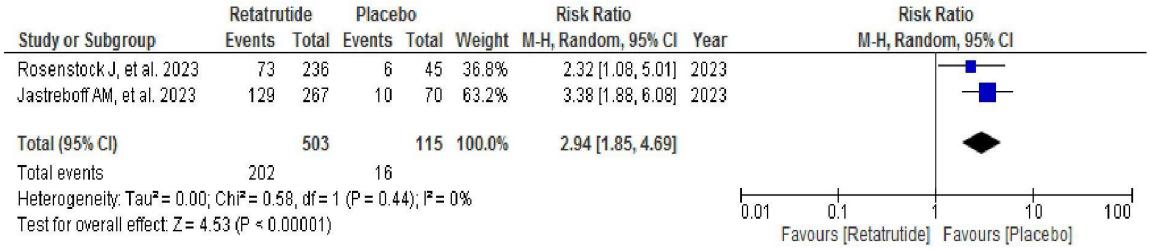

Figure 3b: AEs of special interest

Treatment emergent adverse events occurring in ≥ 5% of total participants

Four studies (Jaestretoff AM, et al. 2023, Rosenstock J, et al. 2023, Urva S, et al. 2022 and Coskun et al. 2022) reported treatment emergent adverse events occurring in ≥5% of total participants and were symptoms of gastrointestinal discomfort, COVID-19, fatigue, urinary tract infection, early satiety, increased lipase levels, headache and eructation. Total numbers of adverse events experienced in the retatrutide arms were 342, 198, 55 and 34 with a total of 268, 236, 57 and 35 participants in these studies, respectively. Total numbers of adverse events experienced in placebo arms were 48, 15, 7 and 3 with a total of 70, 45, 15 and 10 participants in these studies. Pooled results demonstrated a significantly higher risk of common adverse events in the retatrutide group than in the placebo group (RR 2.42; 95% CI 1.77, 3.31; p< 0.0001). Heterogeneity was low with an I^2 value of 0% [Figure 4a].

Treatment emergent adverse events occurring in <5% of total participants

These adverse events included hypertension, nasopharyngitis, dizziness,

abdominal pain, dyspepsia, gastro-esophageal reflux disease, increased blood creatine phosphokinase, headache, sinusitis, urinary tract infection, upper respiratory tract infection, abdominal pain, etc. Pooled results demonstrated a significantly higher risk of common adverse events in the retatrutide group than in the placebo group (RR 1.77; 95% CI 1.33, 2.37; p= 0.0001). Heterogeneity was low with an I^2 value of 0% [Figure 4b].

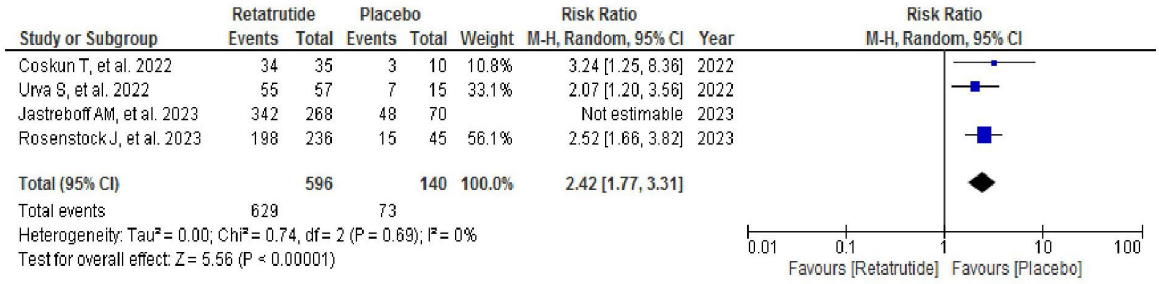

Figure 4a: AEs in ≥5% of total participants

Figure 4b: AEs in <5% of total participants

DISCUSSION

The safety profile of retatrutide, according to the four studies, was overall well-tolerated with certain dose-dependent adverse events. Overall, adverse events most commonly reported in the included studies were gastrointestinal in nature, including nausea, vomiting, diarrhea, and constipation. These effects were more pronounced at higher doses and in general occurred during the dose-escalation phase but were usually mild to moderate in nature and often controlled by dose adjustment.

One of the key findings in relation to SAEs is that such incidences were relatively low in all the retatrutide treatment groups. In the studies by Rosenstock et al. 2023[19], and Urva et al. 2022[17] serious adverse events were reported in approximately 5% of the subjects treated, with no significant difference in SAE risk between the groups treated with retatrutide and placebo. Of note, no subject died from study drug-

related deaths, although one death in each of the studies (Urva et al. 2022[17] & Jastreboff et al. 2023[18]) was recorded; these were due to a motor vehicle accident and drowning and hence unrelated to treatment. The adverse events leading to discontinuation of retatrutide were generally gastrointestinal in nature and more frequent in the higher-dose groups.

The evaluation of adverse events of special interest in the studies by Rosenstock et al. 2023[19] and Jastreboff et al. 2023[18] indicates a significantly increased risk associated with retatrutide compared to placebo. Notably, AESIs included hypersensitivity reactions, cardiac conduction abnormalities, development of anti-drug antibodies, hepato-biliary disorders, gastrointestinal disturbances, hypoglycaemia, pancreatitis, injection site reactions, renal impairment, and depression or suicidal ideation. This elevated risk underscores the necessity for vigilant patient monitoring throughout treatment.

Furthermore, the pooled analysis of treatment-emergent adverse events occurring in ≥5% of participants revealed that retatrutide significantly increased the risk of common adverse events, such as gastrointestinal discomfort and increased lipase levels. Additionally, TEAEs occurring in <5% of participants, including hypertension and dizziness, also demonstrated a significantly higher risk in the retatrutide group. These findings highlight the importance of careful patient selection and the need for comprehensive counseling regarding potential adverse effects when considering retatrutide as a therapeutic option.

Future clinical trials on retatrutide should optimize dosing regimens to mitigate gastrointestinal adverse events, particularly at higher doses. Careful patient selection is essential, especially for those with pre-existing conditions. Routine monitoring for gastrointestinal disturbances, hypoglycaemia, and cardiac abnormalities is crucial, alongside patient education about potential side effects. Large-scale, long-term studies should be initiated to assess the safety profile in diverse populations. Additionally, a multidisciplinary approach involving endocrinologists, dietitians, and mental health professionals is recommended to address both metabolic and psychosocial aspects of treatment, ensuring comprehensive care for patients with type 2 diabetes and obesity.

Clinicians should implement a structured monitoring plan for patients receiving retatrutide, focusing on known adverse event risks while balancing therapeutic benefits. Patient education on recognizing early symptoms of adverse effects and seeking timely intervention can improve treatment adherence and safety. Retatrutide is still under clinical trials, and its potential for approval and real-world use remains undetermined. The current evidence is limited by the small sample size (n=4 studies), short follow-up durations, and lack of long-term safety data. The included studies provide initial insights, but they do not offer a comprehensive assessment of the drug's long-term risks and benefits. Future research should focus on large-scale trials with extended follow-up periods to thoroughly evaluate efficacy and safety. Long-term safety assessments are crucial to detect potential delayed adverse effects. Post-marketing surveillance should be implemented upon approval to monitor real-world outcomes, ensuring continued patient safety and refining clinical use guidelines.

This study is limited by the small number of included studies (n=4) and potential publication and language biases. We cannot generalize the results of this study because of the small number of included studies. Variability in study designs and safety assessments may affect the consistency of the findings. Larger, multicenter trials with diverse populations and extended follow-ups are needed to validate these results.

CONCLUSION

Retatrutide represents a promising advancement in the management of type 2 diabetes and obesity, offering superior weight reduction and metabolic benefits. However, its triplet agonist mechanism increases the incidence of gastrointestinal side effects and hypersensitivity reactions, necessitating long-term safety evaluations. Larger randomized controlled trials with extended follow-ups are crucial to establish its efficacy, safety, and optimal dosing strategies. Regulatory approvals should be pursued with an emphasis on real-world monitoring and patient-specific risk assessment. Retatrutide may be particularly beneficial for patients requiring significant weight loss and metabolic improvement but should be used cautiously in those prone to GI intolerance or hypersensitivity. Future research should focus on refining dosing regimens and identifying patient populations that will derive the greatest benefit while minimizing risks, ensuring its safe and effective integration into diabetes management.

AUTHOR CONTRIBUTIONS

V.M.: Conceptualization, Methodology, Formal analysis, Writing - Original Draft, Supervision. S.S.: Conceptualization, Formal analysis, Writing - Review & Editing. P.K.M.: Methodology, Writing - Review & Editing. S.K.S.: Validation, Data Curation, Visualization. A.K.: Validation, Data Curation, Visualization. R.K.: Conceptualization, Methodology, Formal analysis, Writing - Original Draft, Supervision.

FUNDING SOURCE

None

ACKNOWLEDGMENT

None.

CONFLICT OF INTEREST

There are no conflicts of interest in connection with this article.

REFERENCES

1. Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, et al. Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2022 Nov 1;45(11):2753-2786. doi: 10.2337/dci22-0034. PMID: 36148880; PMCID: PMC10008140.
2. Lingvay I, Sumithran P, Cohen RV, le Roux CW. Obesity management as a primary treatment goal for type 2 diabetes: time to reframe the conversation. Lancet. 2022 Jan 22;399(10322):394-405. doi: 10.1016/S0140-6736(21)01919-X. Epub 2021 Sep 30. Erratum in: Lancet. 2022 Jan 22;399(10322):358. doi: 10.1016/S0140-6736(22)00046-0. PMID: 34600604.
3. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature. 2006 Dec 14;444(7121):840-6. doi: 10.1038/nature05482. PMID: 17167471.
4. American Diabetes Association Professional Practice Committee. 8. Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022 Jan 1;45(Suppl 1):S113-S124. doi: 10.2337/dc22-S008. PMID: 34964843.

5. American Diabetes Association Professional Practice Committee. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022 Jan 1;45(Suppl 1):S125-S143. doi: 10.2337/dc22-S009. PMID: 34964831.
6. Sudlow AC, Le Roux CW, Pournaras DJ. Long-term outcomes of bariatric surgery in patients with diabetes. Expert Rev. Endocrinol. Metab. 2020 May;15(3):141-146. doi: 10.1080/17446651.2020.1754191. Epub 2020 Apr 15. PMID: 32292077.
7. Nauck MA, Meier JJ. Incretin hormones: Their role in health and disease. Diabetes Obes Metab. 2018 Feb;20 Suppl 1:5-21. doi: 10.1111/dom.13129. PMID: 29364588.
8. Asmar M, Asmar A, Simonsen L, Gasbjerg LS, Sparre-Ulrich AH, Rosenkilde MM, et al. The Gluco- and Liporegulatory and Vasodilatory Effects of Glucose-Dependent Insulinotropic Polypeptide (GIP) Are Abolished by an Antagonist of the Human GIP Receptor. Diabetes. 2017 Sep;66(9):2363-2371. doi: 10.2337/db17-0480. Epub 2017 Jun 30. PMID: 28667118.
9. Christensen M, Vedtofte L, Holst JJ, Vilsbøll T, Knop FK. Glucose-dependent insulinotropic polypeptide: a bifunctional glucose-dependent regulator of glucagon and insulin secretion in humans. Diabetes. 2011 Dec;60(12):3103-9. doi: 10.2337/db11-0979. Epub 2011 Oct 7. PMID: 21984584; PMCID: PMC3219957.
10. Heise T, Mari A, DeVries JH, Urva S, Li J, Pratt EJ, et al. Effects of subcutaneous tirzepatide versus placebo or semaglutide on pancreatic islet function and insulin sensitivity in adults with type 2 diabetes: a multicentre, randomised, double-blind, parallel-arm, phase 1 clinical trial. Lancet Diabetes Endocrinol. 2022 Jun;10(6):418-429. doi: 10.1016/S2213-8587(22)00085-7. Epub 2022 Apr 22. PMID: 35468322.
11. Müller TD, Finan B, Clemmensen C, DiMarchi RD, Tschöp MH. The New Biology and Pharmacology of Glucagon. Physiol Rev. 2017 Apr;97(2):721-766. doi: 10.1152/physrev.00025.2016. PMID: 28275047.
12. Conceição-Furber E, Coskun T, Sloop KW, Samms RJ. Is Glucagon Receptor Activation the Thermogenic Solution for Treating Obesity? Front Endocrinol (Lausanne). 2022 Apr 25;13:868037. doi: 10.3389/fendo.2022.868037. PMID: 35547006; PMCID: PMC9081793.
13. Zeigerer A, Sekar R, Kleinert M, Nason S, Habegger KM, Müller TD. Glucagon's Metabolic Action in Health and Disease. Compr Physiol. 2021 Apr 1;11(2):1759-1783. doi: 10.1002/cphy.c200013. PMID: 33792899; PMCID: PMC8513137.
14. Galsgaard KD, Pedersen J, Knop FK, Holst JJ, Wewer Albrechtsen NJ. Glucagon Receptor Signaling and Lipid Metabolism. Front Physiol. 2019 Apr 24;10:413. doi: 10.3389/fphys.2019.00413. PMID: 31068828; PMCID: PMC6491692.
15. Holst JJ, Wewer Albrechtsen NJ, Pedersen J, Knop FK. Glucagon and Amino Acids Are Linked in a Mutual Feedback Cycle: The Liver-α-Cell Axis. Diabetes. 2017 Feb;66(2):235-240. doi: 10.2337/db16-0994. PMID: 28108603.
16. Coskun T, Urva S, Roell WC, Qu H, Loghin C, Moyers JS, et al. LY3437943, a novel triple glucagon, GIP, and GLP-1 receptor agonist for glycemic control and weight loss: From discovery to clinical proof of concept. Cell Metab. 2022 Sep 6;34(9):1234-1247.e9. doi: 10.1016/j.cmet.2022.07.013. Epub 2022 Aug 18. PMID: 35985340.

17. Urva S, Coskun T, Loh MT, Du Y, Thomas MK, Gurbuz S, 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 Nov 26;400(10366):1869-1881. doi: 10.1016/S0140-6736(22)02033-5. Epub 2022 Oct 27. PMID: 36354040.
18. Jastreboff AM, Kaplan LM, Frías JP, Wu Q, Du Y, Gurbuz S, et al. Triple-Hormone-Receptor Agonist Retatrutide for Obesity - A Phase 2 Trial. N Engl J Med. 2023 Aug 10;389(6):514-526. doi: 10.1056/NEJMoa2301972. Epub 2023 Jun 26. PMID: 37366315.
19. Rosenstock J, Frias J, Jastreboff AM, Du Y, Lou J, Gurbuz S, et al. Retatrutide, a GIP, GLP-1 and glucagon receptor agonist, for people with type 2 diabetes: a randomised, double-blind, placebo and active-controlled, parallel-group, phase 2 trial conducted in the USA. Lancet. 2023 Aug 12;402(10401):529-544. doi: 10.1016/S0140-6736(23)01053-X. Epub 2023 Jun 26. PMID: 37385280.