

Retatrutide for the treatment of obesity, obstructive sleep apnea and knee osteoarthritis: Rationale and design of the TRIUMPH registrational clinical trials

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Abstract

Aims: Retatrutide, a novel synthetic molecule, is a triple agonist activating the glucose-dependent insulinotropic polypeptide, glucagon-like peptide-1 and glucagon receptors. The TRIUMPH clinical development program evaluates its safety and efficacy concurrently for the treatment of obesity and two related complications—obstructive sleep apnea (OSA) and knee osteoarthritis (OA). A novel basket trial design simultaneously evaluates retatrutide treatment across these multiple adiposity-related disease states.

Materials and methods: TRIUMPH consists of four Phase 3, multicenter, randomized, double-blind studies assessing weekly subcutaneous retatrutide compared to placebo, in conjunction with healthy diet and physical activity in over 5800 participants. The four trials consist of two weight management basket trials (TRIUMPH-1 and TRIUMPH-2) with OSA and/or OA protocols nested within the weight management trial; one weight management trial in a population with CVD (TRIUMPH-3); and one stand-alone OA trial (TRIUMPH-4). The primary endpoint for weight management is percent change in body weight, for OSA is change in Apnea-Hypopnea Index and for knee OA includes change in the Western Ontario and McMaster Universities Osteoarthritis Index pain subscale score. The basket trial permits independent analysis of weight management, OSA and OA studies with type I error rate controlled at $\alpha = 0.05$, split between the overarching weight management and each basket trial.

Lee M. Kaplan, Virend K. Somers, Carel W. Le Roux and David J. Hunter are representatives for the Retatrutide Steering Committee Members.

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Conclusions: By recruiting participants with shared disease exposures, the TRIUMPH program will assess the safety and efficacy of retatrutide for the treatment of adults with obesity and two of its common complications—OSA and OA.

KEYWORDS

basket design, clinical trial, GLP-1RA, glucagon agonist, knee osteoarthritis, obesity, obstructive sleep apnea, retatrutide, triagonist, triple agonist

1 | INTRODUCTION

Obesity is a burgeoning worldwide epidemic and contributes to the pathogenesis and progression of numerous complications, including obstructive sleep apnea (OSA), osteoarthritis (OA), type 2 diabetes (T2D) and cardiovascular disease (CVD).^{1–6} The role of excess and ectopic adiposity in the onset or worsening of these conditions is well recognized, with those in higher BMI categories (≥ 35 kg/m²) experiencing greater multimorbidity. While there is extensive evidence of improvement in metabolic parameters with even modest weight reductions of 3–10%, some complications of obesity such as OSA or OA, may require more substantial weight reduction to realize clinically meaningful improvements or resolution. Until recently, relatively little was known about the benefits of weight reduction in the range of 10–15%,⁷ because of the limited efficacy and durability of lifestyle-based weight loss interventions and earlier generations of obesity management medications. With the advent of long-acting therapies that include glucagon-like peptide-1 (GLP-1) receptor agonist activity (e.g., semaglutide and the glucose-dependent insulinotropic polypeptide [GIP]/GLP-1 receptor dual agonist tirzepatide), greater and more sustained weight loss has become achievable medically. The STEP-9 study of semaglutide for knee OA pain and the SURMOUNT-OSA study of tirzepatide for OSA, both completed after the initial approval of these medications for weight management, suggest that obesity management medications result in improvements in these complications of obesity; however, additional studies are needed to elucidate the extent of achievable improvements, generalizability to other obesity management medications, and risks of weight regain during long-term treatment.^{8,9}

In dedicated trials in participants with specific complications of obesity, such as T2D, CVD, OSA and OA, weight reduction from therapies that include GLP-1 receptor agonist activity has generally been less than that seen in general obesity trials of the same agents. This difference may reflect differing baseline characteristics of the populations studied, or an effect of the complications themselves to diminish the weight loss response to these drugs. OSA and OA may also compound the cardiovascular risk of obesity by contributing to elevations in blood pressure^{10,11} and high-sensitivity C-reactive protein, a sensitive marker of cardiovascular risk.^{12,13} The interconnected nature of obesity and complications such as OSA and OA has been incorporated into recent definitions of obesity in the literature, where it has been recommended that the diagnosis of clinical obesity requires evidence of altered organ or tissue function, or substantial

age-adjusted limitations of daily activities.¹⁴ There remains a compelling need for more effective obesity interventions that optimize health gains as well as weight reduction, particularly for populations with a high burden of complications and a reduced quality of life. A better understanding is needed of the efficacy of these interventions in treating patients with obesity and complications of obesity such as OSA and OA.

Retatrutide is a novel synthetic molecule that is a triple agonist activating the glucose-dependent insulinotropic polypeptide receptor (GIPR), glucagon-like peptide-1 receptor (GLP-1R) and glucagon receptor (GCGR). In phase 2 trials in individuals with obesity, retatrutide demonstrated a generally favourable safety profile^{15,16} and produced substantial average weight reductions of up to 24% over 48 weeks, a degree of efficacy that may meaningfully impact multiple obesity-related complications.¹⁵ We therefore aim to evaluate its potential to reduce body weight and treat complications in individuals with obesity, with or without OSA, OA, T2D, or CVD in the TRIUMPH phase 3 core regulatory registration studies. Compared to traditional development programs that implement separate studies for each obesity-related indication, the TRIUMPH program includes both traditional and basket trials to allow concurrent evaluation of retatrutide's safety and efficacy in the treatment of obesity, OSA and knee OA pain (Table 1).

A basket trial is a type of clinical trial that evaluates the effect of a single drug across multiple disease states or patient subgroups that share a common feature, such as a biomarker or pathophysiological trait—in this case obesity.¹⁷ This methodology is commonly used in oncology and neurodegenerative disease, where disease understanding has evolved to encompass both the interconnected and heterogeneous nature of diseases (such as a single tumour type that may have multiple molecularly defined subpopulations, or a single mutation that may cause multiple clinical manifestations).^{17–19} The TRIUMPH program is, to our knowledge, the first to use basket trials in the cardio-metabolic therapeutic space. The basket design nests under a single master protocol multiple subtrials, or baskets, each with its own population, endpoints and analysis plan.¹⁷ Appropriate trial design and statistical controls are instituted to allow for independent statistical testing of the overarching trial and each of its baskets to avoid inflating the Type I, or false positive, error rate due to repeated hypothesis testing. Given the shared pathology of obesity and its complications, a basket trial approach is both reasonable and efficient for studying the effect of a single therapy on obesity and its complications like OSA and OA.

TABLE 1 TRIUMPH trial objectives, endpoints, and designs.

	TRIUMPH-1 NCT05929066	TRIUMPH-2 NCT05929079	TRIUMPH-3 NCT05882045	TRIUMPH-4 NCT05931367
Trial population	BMI ≥ 27 kg/m ² without T2D, including subsets of participants with OA of the knee and OSA ^a	BMI ≥ 27 kg/m ² with T2D, including a subset of participants with OSA and without T2D	Class II/III obesity (≥ 35.0 kg/m ²) and established CVD, with and without T2D	BMI ≥ 27 kg/m ² and OA of the knee, without T2D ^a
Primary endpoint	Percent change in body weight; baseline to Week 80	Percent change in body weight; baseline to Week 80	Percent change in body weight; baseline to Week 80	Change in WOMAC pain subscale score; Percent change in body weight; baseline to Week 68
Basket-specific efficacy objective (primary endpoint)	OA: change in WOMAC pain subscale score; baseline to Week 80. OSA: Change in AHI (events per hour); baseline to Week 80	OSA: Change in AHI (events per hour); baseline to Week 80	N/A	N/A
Participants, N	2300 OA basket: 560 OSA basket: 240	1120 OSA basket: 440	1950	435
Treatment arms; randomization; blinding ^b	Retatrutide QW 4, 9, 12 mg, and PBO; 1:1:1:1; double	Retatrutide QW 4, 9, 12 mg, and PBO; 1:1:1:1; double	Retatrutide QW 9, 12 mg, and PBO; 1:1:2; double	Retatrutide QW 9, 12 mg, and PBO; 1:1:1; double
Randomization stratification factors	Basket indication, prediabetes status, sex	Basket indication, type of baseline antihyperglycemic medication, baseline HbA1c, and sex	Diabetes status, sex, SGLT2i use, and participation in DXA substudy	Baseline WOMAC pain severity (severe [≥ 7] and moderate [< 7]), prediabetes status, and sex
Treatment duration	80 weeks ^b	80 weeks ^b	80 weeks ^b	68 weeks
Safety follow-up period	4 weeks	4 weeks	4 weeks	4 weeks
Key secondary endpoint				
Weight reduction at Week 80				
Percent change in body weight with 4 mg vs. placebo	X	X	N/A	N/A
Percent change in body weight in participants with a BMI ≥ 35 kg/m ^{2e}	X	X	N/A	X ^c
Percentage of participants with $\geq 5\%$, $\geq 10\%$, $\geq 15\%$, $\geq 20\%$ and $\geq 25\%$ WL	X	X	X ^d	X ^c
Percentage of participants with $\geq 30\%$ WL	X	N/A	X ^d	X ^c
Percentage of participants with $\geq 35\%$ WL	X	N/A	N/A	N/A
Change in waist circumference	X	X	X ^d	X ^c
Cardiometabolic				
Change in blood pressure	X	X	X	X ^c
Change in lipid parameters	X	X	X	X ^c
Other				
Change in biomarkers of insulin sensitivity and inflammation	X	X	X	X ^c

(Continues)

TABLE 1 (Continued)

	TRIUMPH-1 NCT05929066	TRIUMPH-2 NCT05929079	TRIUMPH-3 NCT05882045	TRIUMPH-4 NCT05931367
Change in glycemic control	X	X	X	X
Change in hsCRP	X	X	X	X ^c
Change in SF-36v2	X	X	X	X ^c
Change in IWQOL-Lite-CT	X	X	X	N/A
OSA				
From baseline to Week 80				
Change in AHI (events/h) with 4 mg	X	X	N/A	N/A
Percent change in AHI	X	X	N/A	N/A
Percentage of participants achieving AHI <5 or AHI 5–14 with ESS ≤10	X	X	N/A	N/A
Achievement of ≥50% decrease in AHI	X	X	N/A	N/A
Change in patient reported sleep related impairment	X	X	N/A	N/A
Percent change in SASHB	N/A	X	N/A	N/A
OA				
From baseline to Weeks 36 and 68				
Change in WOMAC pain subscale score	X ^d	N/A	N/A	X ^{c,d}
From baseline to Weeks 36, 68 and 80				
Change in WOMAC physical function subscale score	X	N/A	N/A	X ^{c,d}
From baseline to Weeks 68 and 80				
Achievement of ≥50% reduction in the WOMAC Pain subscale	X	N/A	N/A	X ^c
Achievement of ≥50% reduction in the WOMAC Physical Function subscale	X	N/A	N/A	X ^c

Abbreviations: AHI, Apnea Hypopnea Index; BMI, body mass index; CVD, cardiovascular disease; ESS, Epworth Sleepiness Scale; HbA1c, glycated haemoglobin; hsCRP, high-sensitivity C-reactive protein; N, number; N/A, not applicable; OA, osteoarthritis; OSA, obstructive sleep apnea; PBO, placebo; QW, once weekly; SASHB, sleep apnea-specific hypoxic burden; SF-36v2, Short Form-36 Version 2 Health Survey; SGLT2i, sodium-glucose transport protein 2 inhibitor; T2D, type 2 diabetes; WL, weight loss; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

^aInclusion required ≥1 obesity complication (e.g., hypertension, dyslipidemia). The randomized study population was designed to include approximately 80% of participants with a BMI of ≥35 kg/m² and 20% with a BMI of 27 to <35 kg/m². Enrolment of female participants was capped at an upper limit of approximately 70%.

^b16 weeks of dose escalation treatment period followed by 64 weeks of maintenance treatment period.

^c68 weeks.

^dWith 9 and 12 mg.

^eAnalyses for the BMI ≥35 subgroup are prespecified and include additional key secondary analyses for this subgroup.

2 | METHODS

The TRIUMPH registration clinical program includes four Phase 3, multicenter, randomized, placebo-controlled, double-blind studies assessing the efficacy and safety of retatrutide administered subcutaneously once weekly compared with placebo, when used in conjunction with a healthy diet and physical activity, to (1) reduce excess body weight and maintain weight reduction long term in adults with obesity or adults who are overweight with at least one complication of obesity, (2) improve moderate-to-severe OSA in adults with obesity or who are overweight and (3) reduce pain from knee OA in adults with obesity or who are overweight (Tables 1 and S1, Supporting Information and Figure 1). The four TRIUMPH trials consist of two 80-week weight management basket trials (TRIUMPH-1 and TRIUMPH-2) with OSA and/or OA protocols nested within the weight management trial; one 80-week weight management trial in a population with CVD (TRIUMPH-3); and one 68-week stand-alone OA trial (TRIUMPH-4). All trials are being conducted in accordance with good clinical practice guidelines and the principles of the Declaration of Helsinki. Independent Ethics Committee or Institutional Review Board approval was received for each participating site. All participants provided written informed consent prior to trial enrolment. Assignment to treatment groups was determined by a computer-generated, random sequence using an interactive web response system (Figure 2).

2.1 | Population

The TRIUMPH program is being conducted across 13 countries including Argentina, Australia, Brazil, Canada, Hungary, India, Mexico, Poland, Romania, Slovakia, Spain, the United Kingdom and the United States. According to recent guidelines, including the Lancet Diabetes and Endocrinology Commission definition of obesity and

Canadian clinical practice guidelines, participants who are overweight and have at least one complication of obesity may be considered to meet the diagnosis of clinical obesity and should be considered for the initiation of obesity management medication; by this definition, all participants included in the TRIUMPH studies with a baseline BMI $<30 \text{ kg/m}^2$ have clinical obesity.^{14,20} Participants are adults ≥ 18 years of age with a history of at least one self-reported unsuccessful effort to reduce body weight by dietary intervention, who have not had a self-reported or documented change in body weight of $>5 \text{ kg}$ within 90 days before screening.

TRIUMPH-1 is a weight management trial in participants with obesity without T2D, while TRIUMPH-2 is a weight management trial in participants with obesity who have a diagnosis of T2D and HbA1c of $\geq 6.5\%$ and $\leq 10.5\%$. Both TRIUMPH-1 and TRIUMPH-2 are basket trials with a nested OSA trial within each that includes participants who have moderate-to-severe sleep apnea with or without exposure to positive airway pressure therapy. TRIUMPH-1 also has a nested OA trial that, similar to the TRIUMPH-4 standalone OA trial, includes participants with obesity with knee pain and radiographic evidence of knee OA. For TRIUMPH-1 and TRIUMPH-2, screening for the weight management master trial and the OA and OSA baskets occurred concurrently. In TRIUMPH-1, participants were allowed to enrol in no more than one basket (either OSA or OA). TRIUMPH-3 is a weight management trial in participants with obesity, with or without T2D, who have established CVD. Additional trial-specific eligibility criteria are presented in Table S1. Enrolment of female participants is capped at approximately 70% to ensure sufficient male representation, given that participants typically seeking enrolment in obesity trials have been disproportionately female. Given the high unmet need in individuals with Class 2 and 3 obesity, the TRIUMPH program is enriched for these participants, with these classes comprising approximately 80% of the TRIUMPH-1 and TRIUMPH-4 studies, and all of the TRIUMPH-3 population.^{21,22} The overall size of the trials, however,

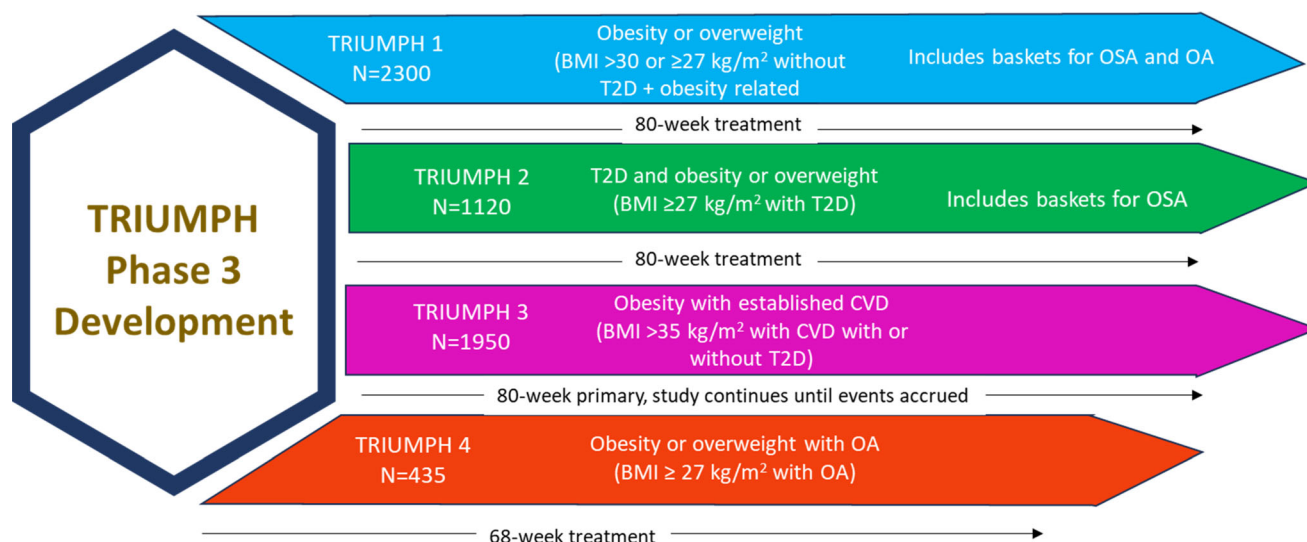


FIGURE 1 TRIUMPH phase 3 program overview. OSA, obstructive sleep apnea; OA, osteoarthritis; BMI, body mass index; T2D, type 2 diabetes; CVD, cardiovascular disease.

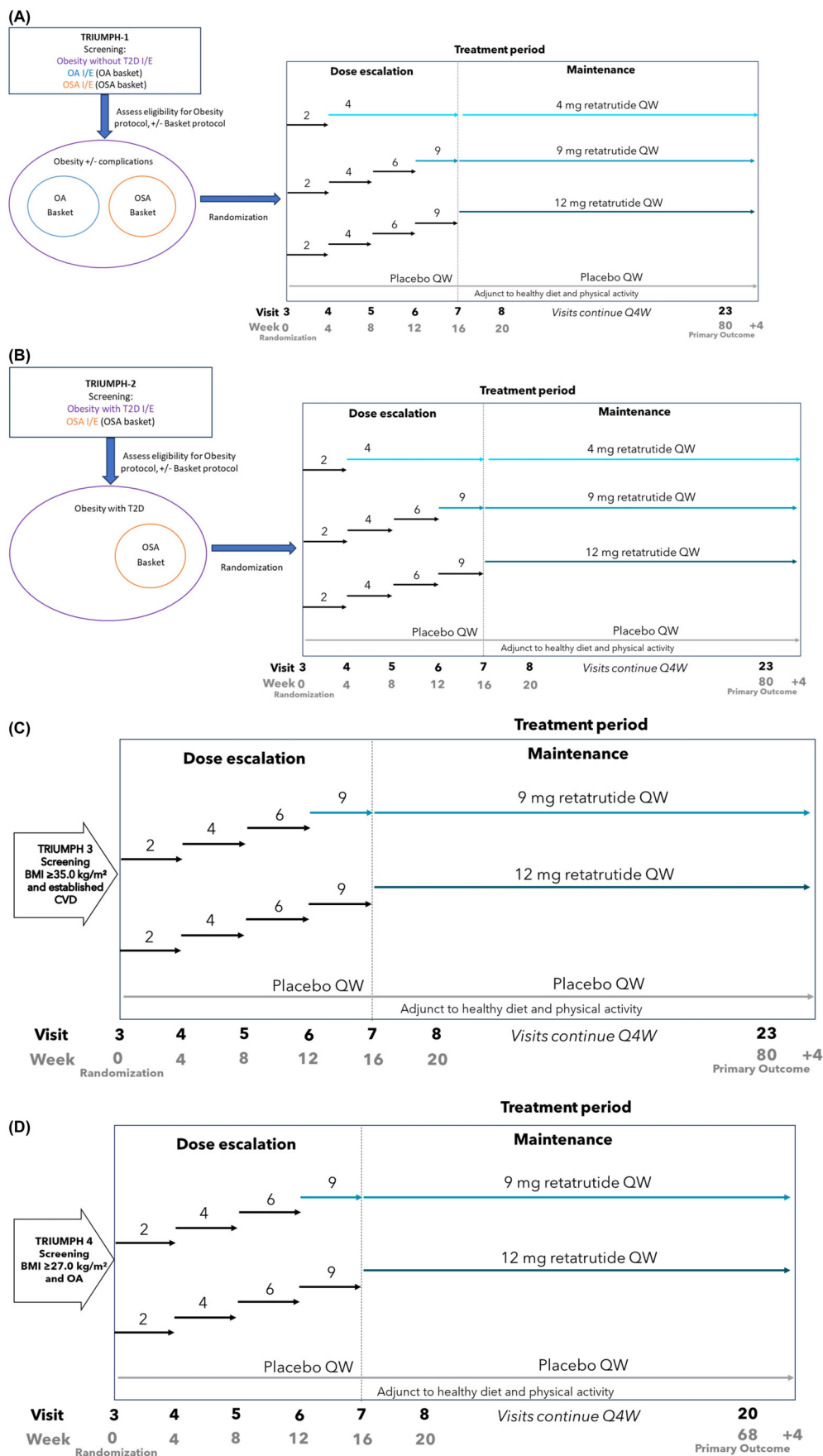


FIGURE 2 Study schematics. (A) TRIUMPH-1, (B) TRIUMPH-2, (C) TRIUMPH-3, (D) TRIUMPH-4. Retatrutide maintenance dose of 4 mg only included in TRIUMPH-1 and TRIUMPH-2. TRIUMPH-4 primary outcome is at Week 68. I/E, inclusion and exclusion; OA, osteoarthritis; OSA, obstructive sleep apnea; QW, once weekly; Q4W, once every 4 weeks; BMI, body mass index; CVD, cardiovascular disease.

allows for a sufficient number of participants who are overweight or have Class 1 obesity to characterize the safety and efficacy of retatrutide in this population.

2.2 | Study intervention

TRIUMPH-1 and TRIUMPH-2 evaluate retatrutide in doses of 4, 9 and 12 mg and placebo comparator given subcutaneously once weekly, while TRIUMPH-3 and TRIUMPH-4 are evaluating retatrutide in weekly doses of 9 and 12 mg and placebo comparator. Randomly assigned doses are achieved through a fixed dose escalation regimen, and participants and study staff are blinded to the assigned study drug. Doses and escalation were selected based on safety and efficacy data as well as exposure-response modelling from phase 1 and 2 retatrutide studies.^{15,16,23} A permanent dose reduction is permitted for management of gastrointestinal adverse events or inadequate oral intake that has not improved with other mitigations, including a prior de-escalation and re-escalation attempt. Dose reduction is also allowed for participants who reach a BMI of $\leq 22 \text{ kg/m}^2$, or who perceive that they have experienced excessive weight loss.

Throughout the TRIUMPH trials, all participants receive individualized lifestyle counselling with an emphasis on a healthy diet and physical activity, as the standard of care. Dietary counselling focuses on healthy dietary content, rather than caloric restriction; recommended dietary patterns emphasize maintaining adequate intake through a macronutrient-balanced diet and nutrient-rich foods. Participants are also counselled to participate in at least 150 min of moderate-intensity physical activity per week that includes a component of muscle-strengthening activities. In order to maintain trial assay sensitivity, allowed use of background concomitant therapies and add-on therapies that have the potential to impact the assessment of efficacy for weight management, glycemic control, management of OSA and management of OA pain are specified in the respective studies (Table S2).

Study drug discontinuation is determined by the participant or investigator. Clinical considerations for discontinuation include but are not limited to pregnancy, adjudication-confirmed pancreatitis, malignancy, a BMI of $\leq 18.5 \text{ kg/m}^2$, treatment with bariatric surgery, or a systemic hypersensitivity reaction. Participants who permanently discontinue the study drug for any reason other than pregnancy are encouraged to remain in the study and adhere to the study schedule. In the event of premature study discontinuation, participants complete a post-treatment safety follow-up assessment. An investigator may temporarily interrupt study intervention, for example, in the event of acute illness, surgery, or hospitalization.

2.3 | Outcome measures

Table 1 describes the primary and secondary endpoints for each trial measured from baseline to end of treatment. The primary obesity endpoint for each trial is the percent change in body weight. Key

secondary endpoints include change in waist circumference, blood pressure, lipid levels and patient-reported health outcomes, as well as glycemic parameters in participants with T2D. Other secondary endpoints include biomarkers of insulin sensitivity and inflammation. In trials for OSA (TRIUMPH-1 and TRIUMPH-2 OSA baskets), the primary endpoint is the change in the Apnea-Hypopnea Index (AHI) (number of apnea and hypopnea events per hour), and secondary endpoints include Patient-Reported Outcomes Measurement Information System Sleep-Related Impairment (PROMIS-SRI), percentage of participants with a $\geq 50\%$ decrease in AHI, and hypoxic burden as assessed by % change in Sleep Apnea-Specific Hypoxic Burden (SASHB). In trials for knee OA (TRIUMPH-1 OA basket and TRIUMPH-4), the primary endpoint includes the average change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale score, and key secondary endpoints include change in the WOMAC physical function subscale score and the percentage of participants with a 50% reduction in the WOMAC pain subscale score. Centrally adjudicated clinical endpoints across the TRIUMPH program include death; nonfatal cardiovascular adverse events including myocardial infarction, hospitalization for unstable angina or heart failure, coronary revascularization, stroke and transient ischemic attack; pancreatitis, and new onset T2D. TRIUMPH-3 includes a sub-study to measure body composition via DXA in approximately 100 participants to assess percent and absolute change in total body fat and lean mass.

2.4 | Assessments

Obesity efficacy assessments of all randomly assigned participants are collected throughout the TRIUMPH program as specified in the protocols and include body weight, waist circumference, blood pressure and lipid and glycemic parameters. For each participant, body weight measurements are collected during the fasted state and on the same scale capable of measuring weight in kilograms to 1 decimal place. Waist circumference is measured in centimetres in the horizontal plane and at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest. A single central lab is used for all laboratory assessments.

For the OSA studies, polysomnography (PSG) assessments are done during overnight clinic stays at screening and weeks 24 and 80 and are scored centrally using the American Academy of Sleep Medicine 1B hypopnea scoring method. Participants on positive airway pressure (PAP) therapy are instructed to suspend use of this treatment for 7–9 days prior to the scheduled PSG assessments to allow for measurement of drug treatment effect unobscured by PAP.^{24–29} AHI events per hour are calculated by adding the total number of apneic and hypopneic episodes and dividing that total by the total sleep time. Other efficacy assessments include measurement of neck circumference, blood oxygen saturation and patient-reported outcomes, as detailed below.

For the knee OA studies, the 24-question WOMAC instrument (Numeric Rating Scale [NRS] version 3.1) is administered at screening,

baseline, periodically throughout the treatment period, and at the last treatment and safety follow-up visit. Participants record their responses using a 0–10 NRS for each question in the pain (5 questions), stiffness (2 questions) and physical function (17 questions) subscales. Each subscale score is calculated by summing the scores of the individual items and converting to a 0–10 scale by dividing it by the number of items in the subscale. Only the WOMAC pain subscale is used for the primary OA endpoint assessment. OA secondary endpoint assessments include change in WOMAC physical function subscale score, average pain intensity NRS score and worst pain intensity NRS score, as well as frequency, timing and amount of concomitant pain medications as recorded in the daily electronic diary. Centrally read posteroanterior modified Lyon-Schuss knee radiographs are performed at screening and study end.

Patient-reported outcome assessments are conducted across the TRIUMPH program. These include the following self-administered questionnaires for general and obesity assessments in all trials: the Short Form 36 Version 2 Health Survey, Patient Global Impression of Severity (PGI-S) Physical Function due to Weight, Patient Global Impression of Change (PGI-C) Physical Function due to Weight, Impact of Weight on Quality of Life-Lite Clinical Trials Version (IWQOL-Lite-CT), Euro-Qol Five-Dimensional Five-Level Questionnaire (EQ-5D-5L) and Power of Food Scale (in TRIUMPH-1 and TRIUMPH-3 only). OSA patient-reported assessments include the ESS, PROMIS-SRI, PROMIS-SD, FOSQ, and the PGI-C and PGI-S for OSA-related sleepiness, fatigue, sleep quality and snoring. Questionnaires for OA assessment include the WOMAC, PGIS-Target Knee Function and Target Knee Pain, PGIC-Target Knee Function and Target Knee Pain, and NRS for average daily pain intensity and worst daily pain intensity.

Safety assessments are conducted throughout the TRIUMPH program as specified in the protocols and include physical examinations, pulse, electrocardiograms and laboratory assessments (including hepatic, renal, pancreatic, calcitonin, haematology and immunogenicity assessments). In addition, participants are monitored for depression, suicidal ideation and behaviour risk through mental health questionnaires (Patient Health Questionnaire-9 and Columbia Suicide Severity Rating Scale). Adverse events and concomitant medication information are collected throughout the trial periods, including the safety follow-up.

2.5 | Statistical analysis

2.5.1 | The basket trials: TRIUMPH-1 and TRIUMPH-2

For TRIUMPH-1 and TRIUMPH-2, the overall type I error rate is controlled at the 0.05 significance level. Alpha is split between the weight management protocol-level analysis ($\alpha = 0.025$) and each basket (each allocated $\alpha = 0.025$). This design accommodates overlapping populations between the weight management and basket populations. In TRIUMPH-1, which has two baskets (OSA and OA), the basket populations overlap with the weight management protocol but do not

overlap each other. The baskets each have distinct primary endpoints and multiplicity control strategies and receive $\alpha = 0.025$. The sample sizes in the baskets of TRIUMPH-1 and TRIUMPH-2 were determined independently of the main trial. For example, the TRIUMPH-1 and TRIUMPH-2 OSA baskets are each designed to provide at least 95% power to demonstrate the superiority of retatrutide 9 and 12 mg versus placebo in the change in AHI, assuming each dose is analysed separately in parallel using a 2-sample *t* test at a 2-sided significance level of 0.0125. Similarly, the sample size in the TRIUMPH-1 knee OA basket is designed to provide at least 90% power to detect a clinically meaningful benefit of retatrutide 9 and 12 mg versus placebo in the change in WOMAC pain subscale score, assuming each dose is analysed separately in parallel using a Satterthwaite *t* test at a 2-sided significance level of 0.0125, accounting for differences that have been observed historically in variability between placebo and active arms.³⁰ The sample sizes for the overarching TRIUMPH-1 and TRIUMPH-2 weight management trials were then determined to ensure the generalizability of study data to the intended patient population with obesity, such that despite the basket design, the percentages of participants with OSA and/or OA in these trials remain representative of the prevalence of these conditions in the general obesity population. These sample sizes also take into consideration expected differences in the amount and variability of weight reduction in participants with and without type 2 diabetes.³¹ The overall TRIUMPH-1 and TRIUMPH-2 sample sizes provide at least 90% power to detect clinically meaningful weight reduction with retatrutide at 9 and 12 mg doses versus placebo on percent change in body weight, assuming each dose is analysed separately in parallel using a 2-sample *t* test at a 2-sided significance level of 0.0125.

2.5.2 | TRIUMPH-3 and TRIUMPH-4

The sample size for TRIUMPH-3 is designed to provide at least 90% power to detect clinically meaningful weight reduction with retatrutide 9 and 12 mg versus placebo on percent change in body weight, assuming each dose is analysed separately in parallel using a 2-sample *t* test at a 2-sided significance level of 0.025.

The sample size for TRIUMPH-4 is designed to provide at least 90% power to demonstrate the superiority of retatrutide 9 and 12 mg over placebo on each of the co-primary endpoints: percent change in body weight and percent change in WOMAC pain subscale score (with similar assumptions as above). The power for each primary endpoint is evaluated independently, in parallel. Each dose will be analysed separately in parallel using a 2-sample *t* test for percent change in body weight and a 2-group Satterthwaite *t* test for change in WOMAC pain subscale score at a 2-sided significance level of 0.025.

2.5.3 | General statistical considerations

Obesity efficacy endpoints will be analysed using data obtained during the treatment period for all randomly assigned participants. Each study, overall and within the respective baskets, will evaluate the

superiority of retatrutide to placebo based on both the treatment regimen and efficacy estimands. The treatment regimen estimand represents the average treatment effect of retatrutide relative to placebo, regardless of study drug discontinuation or use of any prohibited treatments that would confound the assessment; hence, all available valid primary endpoint measures will be used in the analysis, consistent with the intention-to-treat principle. The efficacy estimand represents “on-treatment” efficacy and excludes data obtained from participants who were discontinued from the study drug permanently or who used prohibited treatments that could confound the assessment (Table S2). This excluded data for the primary endpoint measures is imputed as if the participants had remained on treatment. For the assessment of body weight change, the prohibited treatments that could cause confounding include obesity management medications or procedures. For the assessment of AHI, the potential confounders include treatments for weight management and OSA and inadequate PAP washout. For the assessment of WOMAC pain subscale score, the potential confounders include obesity management medications, prohibited knee procedures and excessive use of pain rescue medication.

The treatment effects of interest, including the differences in the respective primary endpoints of interest from baseline to the defined primary timepoint, will be summarized using an analysis of covariance (ANCOVA) for the treatment regimen estimand and a mixed model for repeated measures (MMRM) for the efficacy estimand, both with treatment and strata as fixed effects and the baseline response variable as a covariate. ANCOVA includes 2-way interactions (treatment and strata; treatment and baseline). MMRM also includes a visit factor and 3-way interactions (treatment, strata and visit; treatment, baseline and visit).

3 | DISCUSSION

The TRIUMPH phase 3 registrational program aims to assess the efficacy and safety of retatrutide for the treatment of obesity and for the treatment of OSA and knee OA, complications of obesity that account for substantial obesity morbidity, disability, reduced quality of life and economic burden. The use of basket trials within the core registration program is novel in the cardiometabolic disease space and improves the efficiency and speed with which the impact of obesity treatment on multiple complications can be understood. Basket trials leverage the efficiencies of a master protocol, shared infrastructure, common control arms and smaller sample sizes to support faster evaluation and access to promising treatments with reduced participant exposures to investigative therapies that may be ineffective or carry unknown risk. This approach could also better inform optimal patient selection and shared decision-making in clinical practice. Across the program, broad BMI inclusion criteria, ranging from ≥ 27 kg/m² (TRIUMPH-1, TRIUMPH-2 and TRIUMPH-4) to ≥ 35 kg/m² (TRIUMPH-3), and inclusion of participants with and without T2D and established CVD may contribute to the generalizability of the results. The structure of the program is designed to provide a unique opportunity to understand both the impact of treatment on and potential interactions between

obesity and its common complications, including OSA, OA, T2D and CVD.^{32–35}

All participants in the phase 3 TRIUMPH program receive similar lifestyle counselling, focusing on adequate nutrient intake, healthy dietary patterns and at least 150 min of physical activity per week. In contrast to most prior obesity treatment trials that focused on calorie-reduced diets as the background lifestyle intervention, the recommendations in the TRIUMPH program align with recent guidance on the role of healthy lifestyle interventions in the setting of highly effective obesity management medications.^{36,37}

Although basket trials are recognized by the scientific community and regulatory agencies as robust and valid sources of evidence for the efficacy and safety of an investigational drug, building the overall program structure using both traditional and basket trials required careful clinical and statistical consideration to ensure a robust assessment of all endpoints with appropriate type I error control. The overall program size was influenced by regulatory guidance to establish substantial evidence for an indication, including minimum patient exposures for a weight management indication, the desire to include participants with and without T2D, and conduct of at least two well-controlled trials for each indication (weight management, OSA and OA). With that framework in place, weight management protocols were designed and powered for populations without (TRIUMPH-1) and with T2D (TRIUMPH-2). The predicted weight reduction for each cohort was then used to predict the effect sizes for the primary endpoints in the OSA and OA baskets independently, acknowledging that this approach could underestimate weight loss-independent or drug mechanism-dependent effects, which may additionally contribute to efficacy. Finally, the proportional size of the baskets to the size of the overarching weight management protocol was examined with an aim to mimic the prevalence of that comorbidity in the general population with obesity. A consequence of this approach was the creation of TRIUMPH-4 as a separate, standalone OA pain trial. Due to the anticipated lower weight loss in individuals with T2D, a smaller effect on WOMAC scores for OA pain was expected in a T2D population.³⁰ Including a 90% powered OA basket within TRIUMPH-2 would have disproportionately enriched that weight management protocol for participants with OA compared to the OA prevalence expected in a general obesity population with T2D. Therefore, it was more efficient to conduct a separate OA pain trial to meet the substantial evidence regulatory requirement for two separate trials. TRIUMPH-3 also stands outside the basket structure with a separate aim to understand the efficacy and safety of retatrutide for the treatment of obesity in a population with high unmet need, including participants with class II or III obesity and established CVD.

While using a basket trial design can be more efficient in enabling the evaluation of multiple disease states simultaneously and potentially reducing the size and cost of development programs compared to sequential or separate disease state programs, it does have limitations. Operational challenges arise due to the rapid enrolment of obesity trials given the high prevalence of obesity and associated unmet clinical need. The introduction of baskets requiring the existence and documentation of specific complications of obesity requires careful site selection and training to prevent slowing of enrolment.

Participants in the baskets may also have differential needs to ensure drug adherence and retention that must be anticipated to facilitate appropriate training, consent and coaching for both participants and site staff. It should also be noted that basket trials may not be an optimal design for relatively rare complications for which the basket size to enable adequate statistical power would distort the overall enrolment requirements for the overarching study (in this case, obesity). Finally, sponsors conducting basket trials in the cardiometabolic space should consider that interactions with regulatory agencies to support new drug applications are complex. Multiple therapeutic area divisions within each agency must be engaged simultaneously to ensure alignment with the study design, execution and analysis across the relevant disease states.

Despite these potential challenges, the inclusion of participants with OSA and OA through basket studies in an obesity clinical development program allows for greater representation of selected demographic groups. Traditionally, randomized controlled trials of OSA therapies have included predominantly male subjects. This has resulted in a limited understanding of the effects of OSA therapy in female patients. While the TRIUMPH trials restrict female recruitment to at most 70% of the sample size, in OSA trials, male recruitment is often restricted to at most 70% of the sample size. Even 40% female participation in OSA studies would represent an advance in female recruitment and provide novel insights into the effects of treating OSA in females. In addition, obesity studies are typically under-representative of the elderly population. The design of the basket trial favours inclusion of more participants with OA, facilitating greater recruitment of older participants in the overarching weight management trial.

There remains an unmet need for optimizing weight reduction and health gains in individuals with obesity and its complications, including OSA and OA. As the first obesity registration program to include the simultaneous study of three potential indications, TRIUMPH is designed to provide timely and robust evidence on the safety and efficacy of retatrutide for the treatment of obesity, OSA and knee OA in people with obesity.

AUTHOR CONTRIBUTIONS

DJH, LMK, MAB, AL and KG contributed to the study design. KG, MAB, AL and QW drafted the manuscript. AL, KG and QW are the guarantors of this work and, as such, take responsibility for the integrity of the data and the accuracy of the data analysis. KG, LMK, VKS, CL, DJH, QW, AL, NA and MAB authors participated in interpretation of the data and critical review of the manuscript, had access to the data and approved this manuscript to be submitted for publication.

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CONFLICT OF INTEREST STATEMENT

Lee M. Kaplan declares providing paid consultation to Altimmune, Amgen, AstraZeneca, Boehringer Ingelheim, Cytokine, Ethicon, Kallyope,

The Last Food Fight, Eli Lilly, Neurogastrx, Novo Nordisk, Optum Health, Oxford Medical Products, Perspectum, Pfizer and Sidekick Health. Professor Carel le Roux reports grants from the EU Innovative Medicine Initiative, Irish Research Council, Science Foundation Ireland, Anabio and the Health Research Board. He serves on advisory boards and speakers' panels of Novo Nordisk, Roche, Herbalife, GI Dynamics, Eli Lilly, Johnson & Johnson, Gila, Irish Life Health, Boehringer Ingelheim, Currax, Zealand Pharma, Keyron, AstraZeneca, Arrowhead Pharma, Amgen, AbbVie, Metsera, Nymble, Olympus and Rhythm Pharma. CIR is the Chair of the Irish Society for Nutrition and Metabolism. CIR received stock options as payment for scientific advisory board functions from Metsera and Nymble. CIR provides obesity clinical care in the My Best Weight clinic and Beyond BMI clinic and is a co-owner of these clinics. David J. Hunter is the editor of the osteoarthritis section for UpToDate and co-Editor in Chief of Osteoarthritis and Cartilage. DJH provides consulting advice on scientific advisory boards for Haleon, TLCBio, Novartis, Tissuegene, Sanofi and Enliven. Dr. Virend K. Somers is funded by the National Heart, Lung, and Blood Institute (HL65176, HL168173 and HL160619); has served as a consultant for Jazz Pharmaceuticals, Lilly, Apnimed, Axsome and Mineralys; and is on the Sleep Number Scientific Advisory Board. Kathryn Giblin, Mary Angelyn Bethel, Amy Lalonde, Nadia Ahmad and Qiwei Wu are employees and shareholders of Eli Lilly and Company.

DATA AVAILABILITY STATEMENT

Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date for data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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