TRIAL PROTOCOL

Protocol No. I8F-NS-O003

STOP KNEE-OA Trial

Trial Title:

Effect of Subcutaneous Tirzepatide Once-weekly in Patients with Obesity and Knee Osteoarthritis (STOP KNEE-OA): A Randomized, Double-Blind, Placebo-Controlled Trial

Short Title:

Subcutaneous Tirzepatide Once-weekly in Patients with Obesity and Knee Osteoarthritis (STOP KNEE-OA)

Acronym:

STOP KNEE-OA

Sponsor Name:

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Summary of protocol amendments

Version number	Summary of amendments
Version 1.4 (13 March 2024)	First version of protocol approved by Human Research Ethics Committee
Version 1.5 (17 May 2024)	Protocol amendments included in this version of the protocol were made prior to commencing recruitment. We made several amendments to the protocol to clarify specific trial procedures, and to ensure consistency between the schedule of activities and information presented in visit details. These changes included: • Clarifying that dietitian consultation will occur remotely, using a centralised dietitian service. • Clarifying that Lilly will supply the study drug/placebo to a centralized pharmacy rather than to specific study sites. • Clarify the medication blinding procedures, including that blinding of study drug/placebo will be conducted at the central pharmacy and that blinded dispensing will be managed via the IWRS. • Removing minor inconsistencies between the schedule of activities and the descriptions of each study visit. • Clarifying the process of conducting radiographic assessments of osteoarthritis in the target joint. • Updating advice on administering the drug after a missed dose within 96 hours rather than 72 hours, in line with the updated investigator's brochure. Several minor typographical errors were also amended throughout the protocol.
Version 1.6 (30 August 2024)	Protocol amendments included in this version of the protocol were made prior to commencing recruitment. Amendments included: • Ensuring consistent use of investigator titles throughout the protocol • Ensuring consistent use of terminology when referring to investigator's brochure • Specifying that the medical monitor role may be filled by a senior consultant physician

	• Amending reference to consent requiring an independent witness, unless participant requires external assistance to read the relevant consent documents. • Appropriately specifying a threshold value from screening tests for exclusion due to renal impairment • Clarifying the maximum allowable time between entering the waiting list and commencing screening procedures. • Simplifying stratification based on BMI to include two categories (30-39.9, >40) instead of three categories • Minor change to wording of in description of primary outcome assessment, to align with procedures outline in the schedule of activities. • Clarification of wording used to describe allowable dose modification • Clarifying allowable changes to the day of weekly administration following a missed dose • Clarifying criteria for progressing from Visit 1 to Visit 2 Several minor typographical errors were also amended throughout the protocol.
Version 1.7 (23 October 2024)	Protocol amendments included in this version of the protocol were made prior to the first screening visit. Amendments included: • Updated all in person visits to fasting visits, in visit description and schedule of activities. • Updated exclusion criteria to screen out participants responses to Patient Health Questionnaire (PHQ-9) and Columbia Suicide Severity Rating Scale (C-SSRS) clinical assessment. • Updated schedule of activities to include the to Patient Health Questionnaire (PHQ-9) and Columbia Suicide Severity Rating Scale (C-SSRS) assessment at baseline and throughout the trial. • Updated potential causes for discontinuation to include mental health considerations identified through the Patient Health Questionnaire (PHQ-9) and Columbia Suicide Severity Rating Scale (C-SSRS) assessment • Updated reason for discontinuation to include development of type 2 diabetes mellitus • Clarified that exclusions due to autoimmune abnormality requires that the study doctor deems the patient likely to require systemic glucocorticoid therapy during the next 18 months. Addition of exclusion based on recent chronic systemic glucocorticoid therapy.

	• Updated schedule of activities to reflect addition of study doctor assessment and dispensing of study drug at Visit 8
Version 2.0 (29 November 2024)	• Updated titles/role/affiliations of study investigators • Updated pathology screening tests to remove the requirement for calcitonin and added: triglycerides, low density lipoprotein levels (LDL) and high-density lipoprotein levels (HDL), and magnesium. Thyroid stimulating hormone (TSH) noted in the protocol, now also added to the pathology list at appendix 10.
Version 2.1 (3 April 2025)	• Updated title of data scientist Protocol amendments were to align with the statistical considerations section of the protocol with the full Statistical Analysis Plan. Including: • Clarification of endpoints associated with changes in bodyweight. • Updating the statistical models used for analysis of some endpoints • Clarification that further information on handling of missing data and sensitivity analyses are provided in the full Statistical Analysis Plan document.
Version 2.2 (11 June 2025)	Protocol amendments were to facilitate recruitment via patients deemed eligible for knee replacement in both public and private hospital setting. • Clarification of eligibility and waitlist procedures (Section 7.1) • Addition of subgroup analysis for private and public hospital settings.
Version 2.3 (07 July 2025)	Protocol Amendments were made to expand recruitment opportunities: • Extending allowable timeframe from the waitlist / consent to Visit 1 • Narrowing exclusion of patients who have prior weight loss surgery, to allow inclusion of those who had surgery > 5 years before screening or if • Procedure was reversed > 6 months before screening • Clarification surrounding prior use of and initiation of metformin

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1. Synopsis

Rationale

Guidelines recommend weight loss as a core treatment for knee osteoarthritis in patients with obesity.[1] However, the optimal strategy to promote weight loss in this population remains controversial. Estimates from a network meta-analysis of randomized controlled trials (RCTs) indicate that substantial weight loss resulting from bariatric surgery leads to a 62.7% average reduction in pain in patients with knee osteoarthritis.[2] Although dietary, educational, and other non-invasive weight loss interventions are broadly available to this population, they offer moderate and often transient reductions in body weight – and subsequently lead to less meaningful improvements in pain and function.[2]

Effective medication-assisted weight loss interventions may allow patients with obesity and osteoarthritis to avoid progression to knee replacement, without resorting to more invasive and less widely accessible interventions such as bariatric surgery. Tirzepatide is a glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 receptor (GLP1R) agonist, which has demonstrated potential to induce substantial weight loss in patients with obesity.[3] As such, the trial aims to determine the average treatment effect of once-weekly, subcutaneous tirzepatide versus a placebo at 72 weeks, as an adjunct to lifestyle modification, regardless of any post-randomization events in participants with obesity and moderate-to-severe knee osteoarthritis.

Objectives

Primary objective

To determine if tirzepatide is superior to placebo at reducing the percentage of patients with obesity and knee osteoarthritis who progress to knee replacement.

Secondary objectives

To determine if tirzepatide is superior to placebo at:

- Improving osteoarthritis symptoms, including:
    - Knee pain
    - Knee function
    - Knee stiffness
- Reducing patients' willingness to undergo knee replacement.

Overall trial design

This trial will employ a randomised, double-blinded, parallel group design to determine if once-weekly, subcutaneous tirzepatide is superior to placebo at limiting progression to knee replacement in adult patients without diabetes and with a body-mass index (BMI) of 30kg/m2 or more, who were eligible for unilateral knee replacement to treat moderate-to-severe knee osteoarthritis.

Number of participants and allocation

In total, 352 participants will be randomized in a 1:1 ratio to the tirzepatide and placebo arms of the trial. Participants in both study arms will also receive standardized lifestyle modification advice, including both dietary and physical activity recommendations. Treatment will last for 72-weeks, inclusive of the initial 20-week dose escalation period.

Duration of treatment and follow up.

Enrolled patients will be followed-up for 72 weeks after being randomized, for the analysis of our primary efficacy and safety outcomes. A screening visit will occur 2 weeks prior to randomization, and following randomization participants will be followed via in person visits every 4 weeks during a 20-week dose escalation period. Following this, participants will attend in person visits every 12 weeks until the completion of the study period, with telephone follow up conducted at intervals of 4 weeks between these site visits. Additional long-term follow up is planned out to 520-weeks (i.e.,10 years) via linkage of participant data with the Australian Orthopaedic Association's National Joint Replacement Registry and National Death Index. No additional visits are planned during this passive follow up period.

2. Schedule of activities

Visit Number	1*	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Weeks from randomization	-2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72
Allowable Deviation, Days	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Fasting visit	X	X	X	X	X	X	X	X			X			X			X			X
Physician visit	X	X	X	X	X	X	X	X			X			X			X			X
Nurse visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dietitian visit**		X	X	X	X	X	X	X			X			X			X			X
Telephone visit									X	X		X	X		X	X		X	X	
Administrative procedures																				
Informed consent	X																			
Demographic information	X																			
Randomization		X																		
Waitlist deferral		X																		
Clinical assessments																				
Medical history	X																			
Physical exam	X																			
Vital signs	X	X	X	X	X	X	X	X			X			X			X			X
Height	X																			
Weight	X	X	X	X	X	X	X	X			X			X			X			X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events/Product complaints	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS assessment^^	X	X	X	X	X	X	X	X			X			X			X			X
Patient education and compliance assessment																				
Instructions on study diary use		X																		
Hand out study diary		X	X	X	X	X	X	X			X			X			X			
Retrieve previous study diary			X	X	X	X	X	X			X			X			X			X
Review diary			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Provide diet and exercise instructions		X	X	X	X	X	X	X			X			X			X			
Review diet and exercise goals		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Injection training		X																		
Dispense study drug		X	X	X	X	X	X	X			X			X			X			
Observe patient administer drug		X																		
Return unused/used study drug			X	X	X	X	X	X			X			X			X			X
Surgery-related outcomes																				
Patient-reported knee replacement								X			X			X			X			X
Verify surgery status from EMR								X			X			X			X			X
Query patient for return to waitlist								X			X			X			X			X
Radiographic and laboratory tests																				
Radiographic assessment	X																			
HBA1C	X*																			X
Fasted blood glucose (FBG) test	X*																			
FSH	X																			
Serum pregnancy test	X																			
FBE, U&Es, LFTs, Triglycerides, Lipid Panel, TSH, Mg	X																			
Patient-reported outcomes																				
WOMAC, Likert version 3.1		X			X			X			X			X			X			X
SF-36 Version v1		X			X			X			X			X			X			X
PASE		X			X			X			X			X			X			X
PHQ-9	X							X						X						X

^ The initial screening visit will take place over multiple days, to allow for HbA1C and FBG to be measured on two separate days during the screening period. * HbA1C & FBG will be measured twice across 2 separate non-consecutive days to allow for appropriate screening for (and exclusion of) participants with evidence of T2DM. ** Dietitian consultations will be conducted via telehealth/telephone, using a centralised dietitian service. ^^ C-SSRS assessment to be conducted during in person visits with study doctor. Assessments adapted to remove intensity of ideation and lethality of behaviour sections.

3. Introduction

3.1 Background

Guidelines recommend weight loss as a core treatment for knee osteoarthritis in patients with obesity.[1] However, the optimal strategy to promote weight loss in this population remains controversial. Estimates from a network meta-analysis of randomized controlled trials (RCTs) indicate that substantial weight loss resulting from bariatric surgery leads to a 62.7% average reduction in pain in patients with knee osteoarthritis.[2] A recent RCT demonstrated that people with severe obesity and knee osteoarthritis that underwent bariatric surgery were 25% less likely to progress to total knee replacement within five years than patients receiving usual care.[4] Despite this, clinical and economic constraints mean that bariatric surgery is not available to most patients at immediate risk of progressing to knee replacement. Although dietary, educational, and other non-invasive weight loss interventions are broadly available to this population, they offer moderate and often transient reductions in body weight – and subsequently lead to less meaningful improvements in pain and function.[2]

Effective medication-assisted weight loss interventions may allow patients with obesity to avoid progression to knee replacement, without resorting to more invasive and less widely accessible interventions such as bariatric surgery. In addition to reducing surgery-related morbidity, such interventions may partially mitigate the growing economic burden associated with knee replacement. Due to increasing rates of obesity and aging populations, it is projected that more than 5.5 million knee replacement procedures will be performed in OECD countries each year by 2030.[5] Based on a conservative estimate of US$15,000 per procedure,[6,7] this would result in OECD nations spending approximately US$82 billion each year on direct knee replacement costs. Despite the potential to produce substantial economic savings by reducing reliance on knee replacement in patients with obesity, a recent systematic review identified no trials examining the impact of medication-assisted weight loss on knee osteoarthritis symptoms.[2]

3.2 Trial Rationale

Tirzepatide is a glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 receptor (GLP1R) agonist, which has demonstrated potential as an alternative to bariatric surgery.[3] Evidence from a Phase 3 study (SUMOUNT-1) indicates that once weekly subcutaneous administration of tirzepatide causes substantial, dose-dependent reductions in body weight in adults without diabetes and with body-mass index of ≥30, or ≥27 and at least one weight-related complication.[3] Assessment of safety indicated that adverse events were observed more commonly in participants assigned to treatment with tirzepatide compared to placebo. Adverse events were generally transient and of mild-to-moderate severity, most commonly consisting of nausea, constipation, or diarrhoea. Among participants in the tirzepatide and placebo groups, reported rates of serious adverse events were similar. As once weekly subcutaneous administration of tirzepatide has been shown to produce substantial weight loss, it has the potential to offer symptomatic relief and limit progression to knee replacement among patients with knee osteoarthritis and obesity.

3.3 Assessment of benefits and risks

3.3.1 Benefits

Weight management for participants in both arms will be better than that which is generally available to members of the community. Tirzepatide has also demonstrated efficacy in inducing clinically meaningful bodyweight reductions among patients with obesity in a recent phase 3 trial, which also indicated that tirzepatide is adequately tolerated in this population.[3] In the broader population of patients with obesity, such reductions in excess bodyweight are associated with improvement in weight-related comorbidities.[8] Moreover, substantial weight loss in patients with knee osteoarthritis and obesity has been shown to induce improvements in pain, and reduced reliance on knee replacement.[2,4] Potential reductions in progression to knee replacement may also limit participants exposure to surgical complications.

3.3.2 Risks

As outlined in the investigator's brochure, tirzepatide has the following possible or known risks:

- Injection site reactions
- Gastroesophageal reflux disease
- Fatigue
- Alopecia
- Hypotension and dizziness
- Pancreatitis
- Hypoglycaemia with concomitant use of insulin or insulin secretagogues
- Hypersensitivity or allergic reactions
- Acute Kidney Injury
- Gastrointestinal symptoms including nausea, vomiting, and diarrhoea, constipation, eructation, flatulence, dyspepsia, abdominal distension, abdominal pain
- Diabetic retinopathy
- Acute gallbladder disease

Animal studies have shown that tirzepatide increases the risk of thyroid C-cell tumours in rodents. To date, no events of thyroid malignancies, medullary thyroid carcinoma (MTC), or C-cell hyperplasia have been reported in humans in the tirzepatide clinical development program. While the human relevance of these findings is currently unknown, evidence collected to date suggests that this effect may be specific to rodents.

Studies in animals have shown reproductive toxicity when tirzepatide was administered during organogenesis. While there are currently no well-controlled studies of tirzepatide in pregnant women, this risk is not relevant to study participants as pregnant women and women of reproductive potential will be excluded from this study.

Tirzepatide is known to delay gastric emptying. Based on anecdotal reports, this may increase the risk of regurgitation and pulmonary aspiration of gastric contents during procedures requiring anaesthesia or deep sedation. The risk of aspiration in patients taking GLP-1 receptor agonists has yet to be adequately quantified.

3.3.3 Overall risk-benefit profile

Phase III trials have shown that tirzepatide is generally well tolerated in doses ranging from 5mg to 15mg, with a safety profile that is acceptable given the health benefits associated with clinically meaningful reductions in bodyweight among patients with obesity. Precautions related to many of the known or suspected risks associated with the study drug have been imbedded within the trial design. These precautions include monitoring for certain serious adverse effects (e.g., pancreatitis), exclusion of populations at high risk of certain SAEs from the study sample (e.g., those with MENS-2, diabetes, or serious GI disease), and implementing protocols to manage common GI symptoms.

Additional information on identified and potential risks are outlined in the investigator's brochure.

4. Objectives and Outcomes

4.1 Primary outcome

Objective	Outcome
To determine if tirzepatide is superior to placebo at reducing the percentage of patients that progress to knee replacement in the target joint within 72 weeks	Proportion of patients who undergo knee replacement in the target joint within 72 weeks of randomization

4.2 Secondary outcomes

Objective	Outcome(s)
To determine if tirzepatide is superior to placebo at improving osteoarthritis symptoms	Mean change in Western Ontario and McMaster Universities Arthritis Index (WOMAC): • Pain Score • Function Score • Stiffness Score Each of these scores will be measured as a change from baseline at 72 weeks after randomization.
To determine if tirzepatide is superior to placebo at reducing patients' willingness to undergo knee replacement	Proportion of patients who undergo knee replacement in the target joint within 72 weeks of randomization or re-enter the waiting list within 72 weeks of randomization.
To determine if tirzepatide is superior to placebo at reducing bodyweight	• Mean change in body weight at 72 weeks after randomization. • Proportion of participants with ≥5% body weight reduction at 72 weeks after randomization • Proportion of participants with ≥10% body weight reduction at 72 weeks after randomization • Proportion of participants with ≥20% body weight reduction at 72 weeks after randomization
To determine if tirzepatide is superior to placebo at improving physical and mental health status	• Mean change in SF-36 Physical Component Summary at 72 weeks after randomization. • Mean change in SF-36 Mental Component Summary at 72 weeks after randomization

To determine if tirzepatide is superior to placebo at improving physical activity levels	• Mean change in PASE score at 72 weeks after randomization.
To determine if tirzepatide is superior to placebo at reducing the use of prescription pain medication	• Proportion of participants reporting use of non-opioid prescription analgesics between 68-72 weeks after randomization • Proportion of participants reporting use of prescription opioid analgesics between 68-72 weeks after randomization • Mean change in prescription opioids dose at 72 weeks after randomization.
To determine if tirzepatide is superior to placebo at reducing the proportion of patients that progress to knee replacement over the long-term.	• Proportion of patients who undergo knee replacement in the target joint within 260 weeks of randomization. • Proportion of patients who undergo knee replacement in the target joint within 520 weeks of randomization

4.3 Health economic outcomes

Health economic evaluation will be informed by the analysis of the primary and secondary outcomes and will be conducted from a societal perspective. Health economic analyses of trial data are planned and will be prespecified separately.

5. Trial design

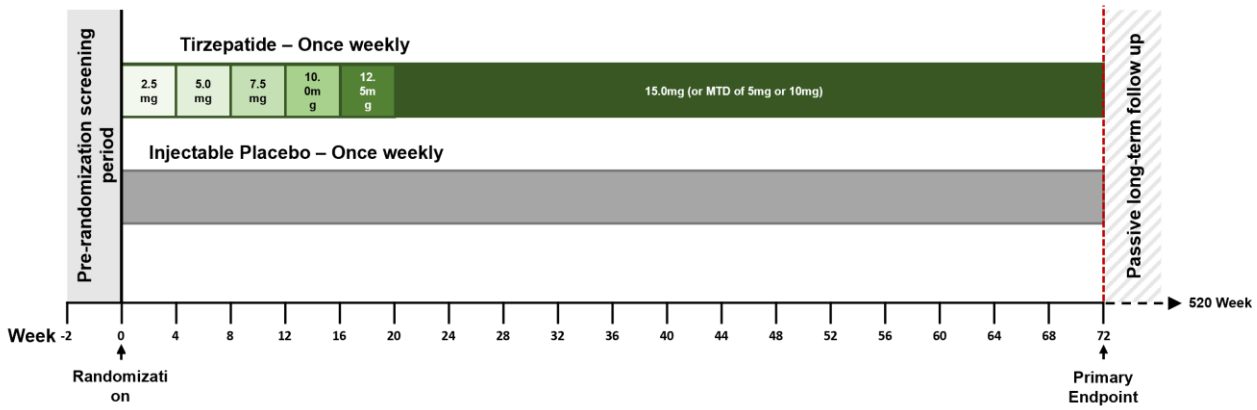
5.1 Overall design

This multicentre phase 4 trial will employ a randomised, double-blinded, parallel group design to determine if once-weekly, subcutaneous tirzepatide is superior to placebo at limiting progression to knee replacement in adult patients without diabetes and with a body-mass index (BMI) of 30kg/m2 or more, who were eligible for unilateral knee replacement to treat moderate-to-severe knee osteoarthritis.

In total, 352 participants will be randomized in a 1:1 ratio to the tirzepatide and placebo arms of the trial. Participants in both study arms will also receive standardized lifestyle modification counselling, including both dietary and physical activity recommendations. Tirzepatide will be initiated at 2.5mg once weekly, with the dose increasing by a further 2.5mg every four weeks until the target weekly dose of 15mg is achieved, or participants reach a lower maximum tolerated dose of 5mg or 10mg. Treatment will last for 72-weeks, inclusive of the initial 20-week dose escalation period.

Enrolled patients will be actively followed-up for 72 weeks after being randomized, for the analysis of our primary efficacy outcomes. Additional long-term follow up is planned out to 520-weeks (i.e.,10 years) via linkage of participant data with the Australian Orthopaedic Association's National Joint Replacement Registry and National Death Index.

Figure 1: STOP KNEE-OA Trial design.



5.2 Scientific rationale for trial design

The duration of treatment (i.e., 72-weeks) and dosing schedule (i.e., once weekly) has been chosen to align with that implemented in a recent phase 3 trial comparing tirzepatide to placebo in patients with obesity and without diabetes.[3] Each of the possible maximum tolerated doses (i.e. 5mg, 10mg, 15mg) have been shown to be effective for weight reduction in this previously published trial.[3] Although 15mg was shown to be the most effective dose for weight reduction in prior trials, participants will be also be permitted to maintain a maximum tolerated dose of 5mg or 10mg as this approach more closely resembles how the study drug would be prescribed in clinical practice. The proposed effect of tirzepatide on osteoarthritis symptoms is expected to be mediated though the study drug's ability to elicit substantial weight loss in the study participants, previous randomized trials indicate that inducing substantial weight loss through bariatric surgery results in clinically important

reductions in pain and reduced progression to total knee replacement in patients with knee osteoarthritis and obesity.[2,4]

The randomised, double-blinded, placebo-controlled design was chosen to minimize bias when evaluating the effect of tirzepatide on each of our study outcomes. As there are currently no effective strategies to promote substantial, sustained weight loss that are considered standard care in people with obesity and knee osteoarthritis (i.e., potential active comparators), this trial will employ a placebo-controlled design to preserve blinding among both patients and study personnel. Although bariatric surgery has been shown to promote weight loss in patients eligible for knee replacement,[4] this surgical intervention has limited application in this population due to restrictions related to age, degree of obesity, and certain medical conditions. In line with current practice, participants in both arms will receive lifestyle modification advice, which will include information relating to increasing physical activity and dietary recommendations.

5.3 Eligibility criteria

5.3.1 Inclusion criteria

Participant will be eligible for inclusion only if they meet all the following criteria:

- Age ≥ 18 years
- Have a body mass index of ≥ 30 kg/m^2.
- Report one or more previous unsuccessful attempt to lose body weight via lifestyle modification.
- Have been deemed eligible to enter the waiting list for primary knee replacement for the treatment of osteoarthritis in the target joint by an orthopaedic surgeon at one of the participating study sites.
- Have moderate-to-severe knee osteoarthritis in the target joint, defined as a Kellgren-Lawrence grade two or greater.
- Be willing to and capable of learning how to self-inject the study drug and follow study procedures for the duration of the trial.
- Provide informed consent to study participation in line with the requirements of the human research ethics committee of the study site.

Female participants must be:

- Not be currently pregnant or breastfeeding **AND**
- Not be of reproductive potential, defined as:
    - Infertile due to surgical sterilization or congenital anomaly, **OR**
    - Post-menopausal defined as:
        - A woman over the age of 40 years with spontaneous cessation of menses for at least 12 consecutive months (in the absence of medications known to induce amenorrhea), with a follicle-stimulating hormone ≥40mIU/mL, and a negative pregnancy test prior to study entry, **OR**

- A woman over the age of 55 years with cessation of menses for at least 12 consecutive months (in the absence of medications known to induce amenorrhea),
  OR
- A woman over the age of 55 years that has commenced hormone replacement therapy after a documented diagnosis of menopause.

5.3.2 Exclusion criteria

Participant will be ineligible for inclusion if they meet any of the following criteria:

- Have been deemed eligible to enter the waiting list for knee replacement in the contralateral knee by an orthopaedic surgeon at one of the participating study sites.
- Have used any prescription medications intended to promote weight loss (e.g., tirzepatide, liraglutide, semaglutide) in the three months prior to screening.
- Have previously undergone any surgical or endoscopic procedure intended to promote weight loss within the last 5 years, with the exception of:
  - Liposuction or abdominoplasty performed > 6months before screening, or if procedure was reversed > 6 months before screening
- Have been diagnosed with type 1 diabetes mellitus (T1DM) or T2DM
- Have laboratory evidence indicative of diabetes mellitus during screening.
- Have personal or family history of medullary thyroid carcinoma (MTC) or Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)
- Have an active malignancy (excluding basal or squamous cell skin cancer).
- Have had a transplanted organ or awaiting an organ transplant
- Have received chronic systemic glucocorticoid therapy (for more than 14 days) in prior 3 months or have a significant, active autoimmune abnormality (e.g., lupus or rheumatoid arthritis) that the study doctor deems likely to require systemic glucocorticoid therapy during the next 18 months.
- Have any other medical conditions, abnormal laboratory tests or concomitant medications that make them unsuitable for participation:
  - Have a clinically significant gastric emptying abnormality.
  - Have had a history of acute or chronic pancreatitis.
  - Have obesity induced by other endocrinologic disorders
  - Have an unstable psychiatric disorder
  - Have a Patient Health Questionnaire (PHQ-9) score of $\geq$15 during screening
  - Have been deemed by the study doctor to be actively suicidal,
    - Have answered “yes” to questions 4 or 5 on the “Suicidal Ideation” section of the Columbia-Suicide Severity Rating Scale (C-SSRS) during screening,
      OR
    - Have answered yes to any questions in the “Suicidal Behaviour” section of the C-SSRS during screening.

AND

- The behaviour or ideation occurred in the last month

  - Have uncontrolled hypertension (systolic blood pressure above or equal to 160 mmHg and/or diastolic blood pressure above or equal to 100 mmHg)
  - Have had within the past 6 months prior to randomisation any of the following: acute myocardial infarction, cerebrovascular accident, unstable angina, or hospitalisation due to congestive cardiac failure (are also exclusion criteria for elective knee replacement)
  - Have severe renal impairment defined as an eGFR <30 mL/min/1.73 m2 at screening visit.
  - Have thyroid-stimulating hormone outside of the range of 0.4 to 6.0 mIU/L at screening visit
  - Have acute or chronic hepatitis or abnormal liver function tests as measured by either alanine aminotransferase or alkaline phosphatase >200 IU.
  - Have any other known contraindication to any glucagon-like peptide-1 receptor agonists.
- Are study site personnel, or immediate family of a member of the study site.
- Have been enrolled in any other study of an investigational product within the past ninety days or are currently enrolled in such a study.

5.3.3 Identification of target joint

In participants with bilateral knee osteoarthritis, the target joint is the knee that they have been deemed eligible to have replaced. All joint-specific study outcomes will be assessed in the target joint unless otherwise specified.

5.3.4 Screening and study consent processes

This trial will enrol patients attending several public hospitals with high volume academic orthopaedic and endocrinology services, in Victoria, Australia. The trial will also enrol participants deemed eligible to undergo surgery in the private hospital setting. Potential participants will be identified upon entry to the elective surgery waiting list for knee replacement.

As part of this process a standard health questionnaire is routinely completed by patients which outlines their medical history, medication usage, height, and weight. The health questionnaire will be used to initially pre-screen participants against the inclusion/exclusion criteria (see 5.3.1 and 5.3.2). Initial pre-screening will be conducted by the study nurse at each study site. Potential participants will be approached by the study nurse, given a verbal explanation of the study, followed by a copy of the Participant Information and Consent Form, and given an opportunity to read it and ask any questions. The patient will be encouraged to discuss the study with an independent source (e.g., Family physician).

If the patient indicates they are willing to consider participation, a formal screening and consent visit will be arranged with the patient within 90 days of entering the waiting list, where they will be seen by a study physician and study nurse. This will be considered study visit 1. Once the patient is satisfied with the information they have received, has had an opportunity to ask questions and obtain additional information, and

the study physician is satisfied that the patient truly understands the nature of the study, the patient will be asked to sign the consent form. Consented participants will undergo clinical and laboratory assessments as outlined in the schedule of activities (Section 2).

Minimal records on participants who are screened but do not meet eligibility or decline to participate at this stage are to be recorded for the purposes of reporting the recruitment process in line with the CONSORT (Consolidated Standards of Reporting Trials) statement. Participants that provide consent to participate in the trial, but who are not randomized, will be considered screening failures. Data on demographics, reasons for screening failure, and any adverse events during the screening process will be collected. Patients that fail screening will not be eligible for rescreening.

5.4 Randomization and blinding

Enrolled patients who meet all eligibility criteria will be randomised using block randomisation in a 1:1 ratio to the tirzepatide or placebo group during their second study visit, using a computer-generated random sequence via the study's Interactive Web Response Systems (IWRS). Randomisation will be stratified according to recruiting site, gender, and body-mass index category (BMI 30-39.9, BMI 40 or more).

Investigators, site personnel, trial monitors, trial statisticians, and participants will be blinded to participant allocation until the last participant has completed their primary efficacy follow-up. The central trial pharmacy will be responsible for blinding all study medications and facilitating delivery to site pharmacies. Tear off labels will be removed at the central pharmacy, prior to study medications being distributed to site pharmacies. At each site, a blinded pharmacist will dispense the study medication to participants using an Interactive Web Response Systems (IWRS) managed by Spiral Web Solutions Limited, which will manage study intervention dispensation in a blinded fashion. The IWRS will be used for the purpose of emergency unblinding when knowledge of the participants assignment is necessary for their medical management. Decisions relating to emergency unblinding will be documented and reported to the trial sponsor.

At the completion of primary follow up, all prespecified data analyses will also be conducted in a blinded fashion. The full statistical analysis plan, including details on secondary analyses for the purposes of long-term follow up or health economic assessments, will be pre-specified and made publicly available prior to the completion of recruitment.

To ensure appropriate monitoring of trial efficacy and safety, the Data Monitoring Committee (DMC) may be unblinded to study allocation for the purposes of interim analyses. Details on the processes to preserve blinding among study personnel are to be outlined in the DMC charter, prior to commencing recruitment for the trial.

5.5 Interventions

Intervention Name	**Tirzepatide**	**Placebo**
Escalation doses	2.5mg, 5mg, 7.5mg, 10 mg, 12.5mg, 15mg	NA
Maintenance doses	5mg, 10mg, 15mg	NA

Route of administration	Subcutaneous	Subcutaneous
Administration Schedule	Once-weekly	Once-weekly
Treatment duration	72 weeks	72 weeks
Source:	Provided by Eli Lilly and dispensed from study sites using Interactive Web Response System (IWRS). The IWRS will be contracted by the investigators and managed by Spiral Web Solutions Limited.	
Packaging:	Study interventions will be administered via pre-filled syringes	
Dose escalation:	During the 20-week dose-escalation period, participants in the active intervention group will be provided with pre-filled syringes containing the relevant incremental dose (ranging from 2.5mg to 12.5mg) prior to commencing the final intended dose.	

5.5.1 Intervention administration

Participants in both study arms will self-administer the pre-filled syringe into the thigh or abdomen on the same day, at approximately the same time, each week. The date and time of administration will be recorded by the participant in their study diary. If a dose is missed, the participant should administer the dose as soon as possible within the next 96-hours. If more than 96-hours has passed since the missed dose, the dose should be skipped and the next dose should be taken at the appropriate day and time. If necessary, the day of weekly administration can be altered if more than 72 hours has elapsed since the last administration. Missed doses should be documented by the participant in the study diary. Both unused study drug and empty syringes should be returned to study site at each visit.

5.5.2 Intervention preparation

Tirzepatide/placebo will be prepared and delivered by Lilly to the central trial pharmacy. The central trial pharmacy will be responsible for blinding all study medications and facilitating delivery to site pharmacies. Pharmacy departments will maintain a log to track receipt of study medication, storage, and distribution. The research team (other than an unblinded pharmacist at the central trial pharmacy) will be blinded to participant allocation. Tear off labels will be removed at the central pharmacy, prior to study medications being distributed to site pharmacies. The participant and all other study personnel will remain blinded to participant allocation. At each site, a blinded pharmacist will dispense the study medication to participants using the Interactive Web-Response System. Emergency unblinding may be performed if a participant's wellbeing requires knowledge of the treatment assignment, through the Interactive Web-Response System.

5.5.3 Dose escalation and modification

Participants in the intervention arm will be initiated at weekly dose of 2.5mg. The dose will then increase by 2.5mg every four weeks until the target weekly dose of 15mg is achieved over the initial twenty-week dose escalation period. Participants who are unable to increase their weekly dose to 15mg will be maintained on the maximum tolerated dose (of 5mg or 10mg) achieved during the escalation period. Dose modification during both the escalation and maintenance phase of the trial is not permissible, unless in response to GI symptoms.

The approach to addressing such symptoms will be adapted from those outlined in a prior phase 3 trial. Participants who experience intolerable GI symptoms will:

- First be counselled to alter dietary behaviours by, for example, having smaller more regular meals or stopping eating when full.
- If such counselling does not alleviate symptoms, participants should be prescribed medications to manage remaining symptoms (e.g., antiemetics, antidiarrheals).
- If symptoms persist, study treatment may be interrupted for up to one dose, prior to recommencing treatment at the same dose. (See section 5.5.8 for details on the management of longer interruptions)
- If symptoms persist, the dose of medication may be reduced by to the next lowest dose of 10mg, 5mg, with multiple dose reductions being permitted.
- Participants that require a reduction below 5mg will discontinue the study drug.
- Dose escalation may continue in the initial 20-week escalation period following a dose reduction, though after this period patients should not continue escalating their dose beyond the MTD achieved in the initial 20 weeks. Throughout the trial, dose escalation should only occur during scheduled visits.

Dose escalation and modification are to be managed via the Interactive Web Response System.

5.5.4 Intervention compliance

Participant compliance will be reviewed at each study visit. Study intervention compliance will be assessed by reviewing administration details recorded in each participant's study diary, accounting of used and un-used study drugs returned at each visit, and direct questioning of study participants. Participants identified as not complying with the study protocol will be provided with additional education on study procedures and encouraged to improve compliance at each study visit. Compliance with lifestyle modification advice will be encouraged in each study visit, with additional specific dietary advice provided as needed during dietitian consultations.

5.5.5 Concomitant Care

In line with guidelines for the management of knee osteoarthritis, participants will also be permitted to use analgesics, as recommended by their primary care physician, throughout the duration of the study, and to engage in additional non-operative treatments for their osteoarthritis (e.g., physiotherapy). Participants will be permitted to use other concomitant medications, if they are not expected to interfere with the assessment of the study intervention (e.g., weight loss medications). Participants are not permitted to undergo concomitant procedures that are expected to interfere with the study intervention (e.g., bariatric procedures).

Glucose control medications may be initiated by participants who develop diabetes while participating in the trial. In line with previous a phase III trial of tirzepatide in non-diabetic patients, initiation of DPP-4 inhibitors or GLP-1R agonists for the treatment of incident diabetes will not be permitted. Metformin should not be initiated for conditions other than diabetes.

5.5.6 Lifestyle modification advice

All participants in the intervention or placebo groups will be provided dietary and physical activity counselling, commencing during the second study visit (i.e., at randomization). Consultations with study dietitians will occur via telehealth/telephone, using a centralised dietitian service. Lifestyle modification advice will focus on making healthy food choices, achieving a 500-kcal deficit per day and 150-300 minutes of moderate-intensity physical activity per week. Calorie deficits will be calculated from participants total energy expenditure, using the following equation:

TEE (kcal/day) = BMR X 1.3

Basal metabolic rate will be calculated based upon the modified WHO equations, outlined in the protocol of the SURMOUNT-1 trial. To promote the maintenance of a healthy weight in study participants, those who reach a BMI of less than 22kg/m2 will be advised to increase their energy expenditure to a maintenance level (i.e., no kcal deficit).

Sex	**Age**	**BMR calculation**
Male	18-30 years	15.057 x weight in kg + 692.2
	31-60 years	11.472 x weight in kg + 873.1
	> 60 years	11.711 x weight in kg + 587.7
Female	18-30 years	14.818 x weight in kg + 486.6
	31-60 years	8.126 x weight in kg + 845.6
	> 60 years	9.082 x weight in kg + 658.5

5.5.7 Intervention discontinuation

In line with the SURMOUNT-1 trial protocol, the study drug may be permanently discontinued for any of the reasons outlined below.

- The participant requests that the study drug be discontinued.
- The participant was inadvertently enrolled despite not meeting all eligibility criteria.
- BMI of below 18.5kg/m2 is reached at any time during the study period.
- Participant becomes pregnant or intends to become pregnant.
- Initiation of open-label GLP-1R agonist/DPP-4 inhibitor and unwilling or unable to discontinue.
- Intolerable GI symptoms, not responding to medical management.
- Participant diagnosed with any of the following after randomisation; T1DM, TD2M, MTC, acute pancreatitis, active malignancy (excluding basal or squamous cell skin cancer).
- Development of a significant study drug-related hypersensitivity reaction.
- Occurrence of any other treatment-emergent AE (TEAE), SAE, or clinically significant finding for which the study physician believes that permanent study drug discontinuation is the appropriate measure to be taken.

- Participant answers "yes" to Question 4 or 5 on the "Suicidal Ideation" portion of the C-SSRS, or "yes" to any of the suicide-related behaviours on the "Suicidal Behaviour" portion of the C-SSRS. Note: The study doctor may seek assistance from a psychiatrist or other relevantly qualified mental health professional to determine if discontinuation is appropriate.
- Participant reports a PHQ-9 score ≥15. Note: Participant should be referred to a mental health professional. If the participant's mental health condition can be adequately managed following referral, they may continue the assigned treatment if deemed appropriate by the study doctor.

Participants who discontinue the study drug but do not withdraw from the study should be encouraged to continue to attend their scheduled study visits. If a participant declines to attend their scheduled visits, they should be encouraged to attend their final visit at 72 weeks after randomization for the purposes of assessing study safety and efficacy outcomes.

5.5.8 Managing Temporary Discontinuation

Interruption of the study drug may be deemed necessary by the investigators or may result from imperfect compliance by the participant. In both instances, the interruption should be documented, and the study drug should be restarted when it is safe to do so, in line with process outlined in the SURMOUNT-1 trial protocol.

Type of interruption	Response
<3 consecutive doses	Restart at last administered dose
≥ 3 consecutive doses	Restart at 5mg and repeat dose escalation
Due to intolerable GI symptoms	See treatment suggestions outlined in section 5.5.3
Due to AE	Document and manage in accordance with section 7.4 of the protocol

5.6 Minimizing loss to follow up.

In instances that the study participant cannot be contacted or has not attended one or more scheduled visits, staff will make concerted efforts to contact the participant via appropriate means. At the completion of the study, linkage with the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) and the National Death Index (NDI) will be conducted to minimize the impact patients that are otherwise non-contactable on the missing primary outcome data.

5.7 Withdrawal from the study

To ensure that loss to follow up is minimized, participants should be both permitted and encouraged to remain enrolled in the study even if they have: discontinued the study drug, have been non-adherent to study drug administration or the study visit schedule, or have stopped the drug due to an adverse event. Participants will be considered to have withdrawn from the trial if they request to be withdrawn from the study and that no further contact be made by study personnel. To minimize the impact of withdrawals on the completeness of primary outcome data, consent will be sought to maintain data linkages with the AOANJRR and NDI among patients who have otherwise withdrawn from participation in the study.

6. Visit structure and participant timelines

6.1 Schedule of activities

Visit Number	1*	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Weeks from randomization	-2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72
Allowable Deviation, Days	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Fasting visit	X	X	X	X	X	X	X	X			X			X			X			X
Physician visit	X	X	X	X	X	X	X	X			X			X			X			X
Nurse visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dietitian visit**		X	X	X	X	X	X	X			X			X			X			X
Telephone visit									X	X		X	X		X	X		X	X	
Administrative procedures																				
Informed consent	X																			
Demographic information	X																			
Randomization		X																		
Waitlist deferral		X																		
Clinical assessments																				
Medical history	X																			
Physical exam	X																			
Vital signs	X	X	X	X	X	X	X	X			X			X			X			X
Height	X																			
Weight	X	X	X	X	X	X	X	X			X			X			X			X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events/Product complaints	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS assessment ^^	X	X	X	X	X	X	X	X			X			X			X			X
Patient education and compliance assessment																				
Instructions on study diary use		X																		
Hand out study diary		X	X	X	X	X	X	X			X			X			X			
Retrieve previous study diary			X	X	X	X	X	X			X			X			X			X
Review diary			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Provide diet and exercise instructions		X	X	X	X	X	X	X			X			X			X			
Review diet and exercise goals		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Injection training		X																		
Dispense study drug		X	X	X	X	X	X	X			X			X			X			
Observe patient administer drug		X																		
Return unused/used study drug			X	X	X	X	X	X			X			X			X			X
Surgery-related outcomes																				
Patient-reported knee replacement								X			X			X			X			X
Verify surgery status from EMR								X			X			X			X			X
Query patient for return to waitlist								X			X			X			X			X
Radiographic and laboratory tests																				
Radiographic assessment	X																			
HBA1C	X*																			X
Fasted blood glucose (FBG) test	X*																			
FSH	X																			
Serum pregnancy test	X																			
FBE, U&Es, LFTs, Triglycerides, Lipid Panel, TSH, Mg	X																			
Patient-reported outcomes																				
WOMAC, Likert version 3.1		X			X			X			X			X			X			X
SF-36 Version v1		X			X			X			X			X			X			X
PASE		X			X			X			X			X			X			X
PHQ-9	X							X						X						X

^ The initial screening visit will take place over multiple days, to allow for HbA1C and FBG to be measured on two separate days during the screening period. * HbA1C and FBG will be measured twice across two separate non-consecutive days to allow for appropriate screening (and exclusion of) participants with evidence of T2DM. ** Dietitian consultations will be conducted via telehealth/telephone, using a centralised dietitian service. ^^ C-SSRS assessment to be conducted during in person visits with study doctor. Assessments adapted to remove intensity of ideation and lethality of behaviour sections.

6.2 Visits structure

Preliminary screening of all patients who are deemed eligible for knee replacement by an orthopaedic surgeon will be conducted by the study coordinating nurse at each site. This will involve review of the patient's existing medical record, radiology, pathology, and routine health questionnaire (which includes height and weight), against the study eligibility criteria (Section 5.3). Patients meeting initial inclusion criteria will be provided with verbal and written material during or immediately following this orthopaedic outpatient visit, given an opportunity to ask questions and if willing, will be contacted (by phone) to inquire if they would like to attend a screening visit. All subsequent visits outlined below will adhere to the schedule of activities (Section 6.1) All activities outlined below will be recorded on the electronic case report form, by the study personnel assigned to complete the activity at the date and time the activity is completed.

6.2.1 Visit 1: Screening

The purpose of Visit 1 is to formally establish eligibility and obtain informed consent. This visit will occur within 90 days of entering the waiting list and will occur over two non-consecutive days, and the patient should be fasted prior to each attendance. As such, when scheduling this visit the participants should be advised not to eat or drink anything other than water in the 8-hours prior to arriving or consume alcohol in the 24-hours prior to arriving. During the first day of the screening visit, participant written informed consent will be obtained prior to arranging screening bloods and imaging and recording of vital signs, height, and weight. The study physician will then obtain a medical history, conduct a physical examination, undertake Columbia-Suicide Severity Rating Scale (C-SSRS) assessment, record concomitant medications, and review vital signs, height, weight, screening bloods, and responses to mental health questionnaires

During the second day of the screening, participants will only be required to have a second round of fasting blood glucose and HbA1c bloods taken, to allow for patients with evidence of T2DM to be excluded. Participants will be excluded if any laboratory evidence suggestive of diabetes (i.e., Fasting glucose: ≥7.0 mmol/L or HbA1c ≥6.5% [48mmol/mol]) is detected, in either the first or second round of screening bloods.

Participants meeting all inclusion criteria (Section 5.3.1) and none of the exclusion criteria (Section 5.3.2) based on the information available, prior to taking scheduled laboratory tests will proceed to Visit 2 within 2 weeks. As laboratory results may not be available prior to the end of this visit, final inclusion of participants will be determined at the beginning of the next visit.

6.2.2 Visit 2: Randomisation

Prior to commencement of any study procedures relating to randomisation, final eligibility criteria based on results that were pending at the end of Visit 1 will be reviewed. This will be a fasted visit. As such, when scheduling this visit the participants should be advised not to eat or drink anything other than water in the 8-hours prior to arriving. Participants that are excluded based on these lab results will be reviewed by a study physician, and any ongoing management of newly diagnosed conditions (e.g., T2DM) will be arranged.

The primary purpose of Visit 2 is participant randomisation, patient education, dispensing and administering study drug and to capture baseline patient reported outcomes. Randomisation will occur immediately following

confirmation of all eligibility criteria, using the study's Interactive Web Response Systems (IWRS). The study coordinating nurse will record vital signs, height, weight, and concomitant medications, collect patient reported outcome measures, and coordinate dispensing of study drug through pharmacy. Participants will then be dispensed the first 4-weeks supply of the study drug from the hospital pharmacy, using the Interactive Web Response Systems (IWRS). The study nurse will then provide training in the administration of the prefilled syringes, observe participant administer drug, hand out the study diary, and provide instructions on study diary use. The dietitian will establish diet and exercise goals in line with the lifestyle modification advice described in Section 5.5.6.

At the end of this visit the study site coordinating nurse will arrange for the participant's status on the waiting list to be converted from "ready for care/scheduled" to "deferred" (see Section 7.1).

6.2.3 Visit 3 to visit 7: Dose escalation period

During the dose escalation period participants will be reviewed face-to-face every 4 weeks by the study physician, and site study nurse. These will be fasted visits. As such, when scheduling this visit the participants should be advised not to eat or drink anything other than water in the 8-hours prior to arriving. Dietitian review will occur remotely. Vital signs, weight, concomitant medications, adverse events, and product complaints will be recorded by the study nurse and reviewed by the study physician during their clinical assessment of the participant (Section 6.1). The study nurse will coordinate dispensing and returning of unused study drug, and will hand out, retrieve, and review participant study diaries. The dietitian will review diet and exercise goals with the participant. At Visit 5 (12 weeks post randomisation), the study nurse will additionally collect questionnaires and patient reported outcome measures.

6.2.4 Visit 8 to visit 19: Treatment period

Face-to-face visits will be scheduled to occur every 12 weeks commencing Visit 8 (24 weeks post randomisation), through to Visit 17 (60 weeks post randomisation). These will be fasted visits. As such, when scheduling this visit the participants should be advised not to eat or drink anything other than water in the 8-hours prior to arriving. During these visits participants will be seen by the study physician and site study nurse as outlined in the schedule of activities. Dietitian review will occur remotely. Vital signs, weight, concomitant medications, adverse events, and product complaints will be recorded by the study nurse and reviewed by the study physician during their clinical assessment of the participant (Section 6.1). The study physician should address any concomitant medications (e.g., antihypertensives) that require alteration as a result of any comorbidities (e.g., hypertension) that have improved or resolved during the study. The study nurse will coordinate dispensing/returning of unused study drug, will hand out, retrieve, and review participant study diaries and collect questionnaires and patient reported outcome measures. The dietitian will review diet and exercise goals with the participant.

The study nurse will ask whether the participant has undergone knee replacement, verify this with the hospital medical record, and confirm with the participant whether they are willing to remain "deferred" on the waiting list (Section 7.1). If the participant declines to remain "deferred", the study nurse will arrange for their surgery

status to be converted to “ready for care/scheduled” and progression to surgery will be managed by each site’s standard waiting list procedures, which follow the principle of patients being treated in turn. The participant will continue to be followed up at all scheduled study visits (Section 6.1).

Eight telephone visits will be scheduled at 4 weekly intervals between face-to-face visits, commencing Visit 9 (28 weeks post randomisation) until Visit 19 (68 weeks post randomisation). Telephone follow-up will be performed by the study nurse. The purpose of these visits will be to record adverse events and product complaints, record concomitant medications, review participant diary entries and diet and exercise goals. Study activities during telephone visits are outlined in the schedule of activities.

6.2.5 Visit 20: Final visit

Visit 20 (week 72 post-randomization) will be the final study visit. This will be a fasted visit. As such, when scheduling this visit the participants should be advised not to eat or drink anything other than water in the 8-hours prior to arriving. During this visit participants will be seen by the study physician and site study nurse. The final dietitian review will be conducted remotely. Weight, concomitant medications, adverse events, and product complaints will be recorded by the study nurse and reviewed by the study physician during their final clinical assessment of the participant. Pathology will be arranged by the study nurse and reviewed by the study physician. The study nurse will coordinate the return of any unused study drug, will retrieve, and review participant study diaries and collect questionnaires and patient reported outcome measures. The dietitian will develop a long-term diet and exercise plan and make ongoing referral to a local dietitian with the participant if deemed appropriate. The study nurse will ask whether the participant has undergone knee replacement and verify this with the hospital medical record. At this final visit the study nurse will confirm with the participant that they wish to remain on or be removed from the waiting list for knee replacement. If the participant choses to remain on the waiting list, the study nurse will arrange for their surgery status to be converted to “ready for care/scheduled” and progression to surgery will be managed by each site’s standard waiting list procedures, which follow the principle of patients being treated in turn.

6.2.6 Visit following premature treatment discontinuation.

If during a scheduled in-person visit, a participant is unable or unwilling to continue the study treatment for any reason, this visit will follow the same structure as their originally scheduled visit, though the participant will be queried about the reason for discontinuation and all remaining study drug should be returned to the trial site. If a participant notifies study staff that they are unable or unwilling to continue treatment outside of an in-person visit, the participant should attend their next scheduled visit in person. The visit will follow the same structure as their next scheduled in-person visit, though the participant will be queried about the reason for discontinuation and all remaining study drug should be returned to the trial site.

Irrespective of when a participant discontinues the study drug, they will be encouraged to attend all subsequent visits. If a participant is unwilling to attend all subsequent visits, they will be encouraged to attend the final visits at 72-weeks after randomization to collect all primary efficacy and safety data.

7. Study Assessment and Procedures

7.1 Management of orthopaedic waiting list

Standard practice is such that upon consent by an Orthopaedic Surgeon for knee replacement at a public hospital, patients are entered onto the hospital's centrally administered waiting list and are flagged as ready for care/scheduled (see definitions below). Patients deemed eligible to undergo surgery by a consultant in a private hospital setting do not enter a centrally administered waiting list, as scheduling is managed directly by the private surgeon and their administrative team. To ensure standardized processes are implemented across public and private settings, this protocol defines the date a patient is formally deemed eligible for primary knee replacement by an orthopaedic surgeon at any participating site as the date that the patient enters the "waiting list" for surgery. All participants enrolled in this trial will have their status on the waiting list converted to "deferred" at their randomization visit. During the study consent process, and at randomization, participants will be advised that this deferral is expected to last at least four weeks after the end of the twenty-week dose escalation period. At the end of this period and at each subsequent in person visit, participants will be asked if they would like their waiting list status to remain "deferred" or reverted to "ready for care/scheduled" with the knowledge that this means that they would be willing to undergo their procedure immediately. Progress to surgery in participants that revert to "ready for care/scheduled" will be managed by each site's standard wait list procedures, which generally follows the principal of patients being treated in turn. Management of this process will be conducted via communication with the centrally administered waiting list staff in the public hospital setting, and via direct communication with the surgeon and their administrative staff in the private hospital setting.

Waiting List Staging	Definition
Ready for Care/ Scheduled	Patient medically fit and willing to undergo KR (knee replacement) immediately if offered a date for surgery
Deferred	Patient medically fit but willing to defer KR until next in person study visit.
Unfit	Medically unfit to undergo KR per physician assessment
Removed	No longer willing to proceed with KR

7.2 Primary outcome assessment

The primary outcome of this study is progression to knee replacement within 72 weeks of randomization. At each in-person study visit following the dose escalation period, the participant will be asked if they have undergone a knee replacement procedure in the target joint, and if so the date of the procedure. For patients that report having undergone a relevant procedure, the patient's hospital records will be reviewed to verify

their surgery status on the day of the relevant in-person visit. At final follow up, each patients hospital medical records will also be reviewed to verify their surgery status and the date of any relevant procedures.

To ensure completeness of follow up and to verify our primary outcome assessment, particularly in instances where patients may have had their joint replaced at a non-study site, linkage to the AOANJRR at the end of primary follow up is planned.

7.3 Secondary outcome assessments

7.3.1 Patient-reported outcomes

All patient reported outcomes will be completed upon first arriving at study visits, in line with the schedule of activities. To ensure the completeness of each survey, study staff will review each survey for missing responses, and prompt participants to address any incomplete fields. Participants whose preferred language is not English will be offered surveys translated into their preferred language.

Western Ontario McMaster Osteoarthritis Index (WOMAC)

The Western Ontario McMaster Osteoarthritis Index (WOMAC) is a self-administered questionnaire that measures the respondent's pain, stiffness, and functional limitation associated with their condition. The standard, 48-hour recall version of the survey will be used. It is recommended as a core outcome measure for trials of knee osteoarthritis, which consists of 24 items covering three subscales:

- Pain (5 items),
- Stiffness (2 items),
- Physical Function (17 items).

The 5-point Likert version of the most up-to-date iteration of the survey (Version 3.1.) will be used at all study sites. All WOMAC scores will be converted to a 0-100 scale (0 represents no symptoms; 100 represents extreme symptoms). The prespecified MCID values are: 9 points for the pain score, 7 points for the stiffness score, and 6 points for the function score.[9] Each of these scores will be assessed as change from baseline scores at 72 weeks follow up.

The WOMAC questionnaire will be administered during in-person visits: Visit 2 (Week 0, Pre-randomisation), Visits 5 (Week 12), 8 (Week 24), 11 (Week 36), 14 (Week 48), 17 (Week 60) and 20 (Week 72, final Visit).

36-Item Short Form Survey (SF-36)

The 36-Item Short Form Survey (SF-36) is a self-administered questionnaire that measures eight domains of physical and mental health:

- General health
- Physical Functioning
- Role-physical
- Bodily Pain

- Role-emotional
- Social Functioning
- Vitality
- Mental Health

Responses to the 36-items of the survey are used to calculate the physical component summary (PCS) and mental component summary (MCS) component summary scores. Both summary scores are presented on a 0-100 scale (0 represents worst possible health status; 100 represents best possible health status). The prespecified MCID values are: 5 points for the MCS and 6 points for the PCS.[10] Each of these summary scores will be assessed as change from baseline scores at 72 weeks follow up.

The SF-36 questionnaire will be administered during in-person visits: Visit 2 (Week 0, Pre-randomisation), Visits 5 (Week 12), 8 (Week 24), 11 (Week 36), 14 (Week 48), 17 (Week 60) and 20 (Week 72, final Visit).

Physical Activity Scale for the Elderly (PASE)

The PASE survey measures self-reported physical activity in older adults, includes 12 questions about leisure, household activity, and work-related activity in the seven days prior to administration. Scores range from 0 to 793, with higher scores indicating greater levels of physical activity. MCID values in participants with musculoskeletal conditions are unknown. Each of these summary scores will be assessed as change from baseline scores at 72 weeks follow up.

The PASE questionnaire will be administered during in-person visits: Visit 2 (Week 0, Pre-randomisation), Visits 5 (Week 12), 8 (Week 24), 11 (Week 36), 14 (Week 48), 17 (Week 60) and 20 (Week 72, final Visit).

7.3.2 Willingness to undergo knee replacement.

In addition to assessing progression to knee replacement, we will also assess a composite outcome of progression to surgery or requesting to be made “ready for care/scheduled” on the knee replacement waiting list at any time during 72-week follow up period. This composite outcome is designed to determine if the primary outcome is influenced by delays in gaining access to knee replacement that are external to the effect of the study drug. The first criteria of this composite outcome (i.e., progression to surgery) will be measured as outlined in the primary outcome assessment description (Section 7.2). Following the dose escalation period, participants will be asked if they would like to be reverted to “ready for care/scheduled” on the waiting list at each of the in-person visits, with the knowledge that this means that they would be willing to undergo their procedure immediately. In addition to querying waiting list status directly with participants during their in-person visits, waiting list and other administrative records at all study sites will also be manually reviewed at the end of the primary follow up period.

7.3.3 Body weight reduction

Body weight will be collected during all in-person study visits as outlined in the schedule of activities. To ensure consistency, participants will be weighed with an empty bladder using a calibrated electronic scale will be used in accordance with the manufacturer’s instructions. The participants weight will be recorded in

kilograms, to one decimal place. Participants should remove their shoes, and any outwear and remove anything from their pockets. To maximise the consistency of the baseline and final follow up measurements, participants should be advised not to eat or drink anything other than water in the 8-hours prior to arriving to Visit 2 and Visit 20. Body weight outcomes will be assessed as a percentage change from baseline, and as the proportion of patients achieving predefined thresholds of weight loss.

7.3.4 Prescription analgesic use

Participants will be asked to report the use of any prescription analgesics in the prior four weeks, at randomization and the final in person visit (i.e., at 72 weeks). The type, dose, and frequency of use of all prescription analgesics will be recorded. Opioid and non-opioid analgesic use will be reported separately. These outcomes will be measured as the percentage of patients reporting any prescription opioid/non-opioid analgesics use between 68 to 72 weeks after randomization.

For opioid analgesics, we will also assess the change from baseline prescription opioids dose at 72 weeks after randomization. Prescription opioid dose will be quantified in Oral Morphine Equivalents per day, which will be calculated by summing the total Oral Morphine Equivalent of opioids consumed by the patient in the prior four weeks, divided by 28 days. Oral morphine equivalent doses will be calculated using published conversion factors.

7.4 Adverse events and serious adverse events

7.4.1 Definitions and identification

Investigators are responsible for monitoring the safety of all study participants, as outlined by the National Health and Medical Research Council's (2016) guidance on "Safety monitoring and reporting in clinical trials involving therapeutic goods".[11] Investigators are responsible for ensuring appropriate medical care is provided to participants during the study, which includes proactively following up and providing appropriate care for any adverse events, regardless of severity. A medical monitor who is a senior consultant physician or endocrinologist will be available to advise study personal on the management of severe side effects of concern.

In line with this guidance, for the purposes of this trial adverse events (AEs) are defined as any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and that does not necessarily have a causal relationship with this treatment. Day-to-day fluctuations in pre-existing conditions, pre-planned surgical or non-surgical procedures for conditions that have not worsened from baseline, and lack of drug effect are not classified as AEs for the purpose of this trial.

Serious adverse events (SAEs) are defined as any AE that results in death, is life-threatening, requires unplanned hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. In order for an SAE to be considered life threatening, it must have posed a threat to the life at the time in which it occurred (rather than hypothetically posing a threat to life if the AE were more severe). Hospitalisation for elective treatment of a pre-existing condition that has not worsened from baseline is not considered an SAE.

Participants will be asked non-directive, open-ended questions at each study visit to elicit any potential adverse effects without introducing bias. They will also be asked if they have been hospitalized or commenced any new medications since their last visit. Adverse events may also be identified from other sources, such as hospital medical records, correspondence with other clinicians (e.g., GPs) or laboratory result.

All AEs that occur after the participant has signed the informed consent documents must be recorded by study personnel via the eCRF and assessed against the criteria for being deemed an SAE. It is the responsibility of the investigator to review all relevant documentation (e.g., hospital progress notes, laboratory reports) related to the event. Having reviewed this information, it is the responsibility of the investigator to interpret and document whether a causal relationship between trial drug and any AE/SAE is a reasonable possibility.

Following such assessment, a SAE will be deemed a Suspected Unexpected Serious Adverse Reaction (SUSAR) if it has a reasonable possibility of a causal relationship with the study drug and are not listed in the investigator's brochure.

Any safety-related concern that could negatively affect the participant safety or the continued ethical acceptability or conduct of the trial, will be deemed a significant safety issue (SSI). SSIs where any measure was required to be taken to eliminate an immediate hazard to a participant's safety is deemed an urgent safety matter (USM).

7.4.2 Safety reporting

The site lead investigator at each site is responsible for documenting all safety events that relate to participants recruited at their site. Site leads are responsible for reporting the following safety events to the coordinating principal investigator within 24 hours.

- USMs
- SUSARs
- SAEs (including those determined to be adverse reactions)

Site leads are responsible for reporting the abovementioned safety events to their local HREC or research governance office within 72-hours of becoming aware of the event. Additional institutional reporting requirements may apply to individual sites, as determined by their local governance office.

The coordinating principal investigator is responsible for assessing and categorising all reported safety events, and reporting these to the approving HREC, TGA, and all site leads in line with the National Health and Medical Research Council's guidance on "Safety monitoring and reporting in clinical trials involving therapeutic goods".[11] Additional requirements may apply if deemed necessary by the approving HREC or governance unit.

The coordinating principal investigator is responsible for reporting to the approving HREC, TGA, and all site leads, the following:

- For all USMs, within 72-hours of being made aware of the issue.

- For all other SSIs, within 15 days of becoming aware of the issue.
    - For all SSIs requiring a protocol amendment, amendments must also be submitted to the approving HREC without undue delay and no later than 15 calendar days of decision to halt.
- For all SSIs resulting in the suspension or termination of the trial due to safety concerns, details on the reason and expected duration of these measures without undue delay and no later than 15 calendar days of decision to halt. The abovementioned parties must also be advised of when a trial that has been halted will be restarted.

The coordinating principal investigator is responsible for reporting to the TGA, the following:

- All life threatening SUSARs withing 7 calendar days of becoming aware of the issue
- Non-life threatening SUSARs within 15 calendar days of becoming aware of the issue

The coordinating principal investigator is responsible for reporting to the approving HREC, the following:

- Annual safety reports
- Any updates to the investigator's brochure

7.5 Long term follow-up

In person and telephone visits with participants will cease at the end of the primary follow up period (i.e., at 72 weeks after randomization). To assess the long-term effect of treatment on progression to knee replacement, participants data will be linked with the AOA NJRR to allow for long-term passive follow up of the primary outcome (i.e., undergoing knee replacement surgery in the index joint) and the NDI to provide information on death as a competing risk. Analyses of these data will be conducted at 260-weeks and 520-weeks follow up.

8. Statistical considerations

Further details on the planned analysis will be provided in the statistical analysis plan.

8.1 Statistical hypotheses

The alternative hypothesis for the primary objective of the trial is:

- H_1: Once-weekly, subcutaneous tirzepatide is superior to placebo at reducing the percentage of patients that progress to knee replacement in the target joint within 72 weeks.

The alternative hypotheses for the secondary objectives of the trial are:

- H_1: Once-weekly, subcutaneous tirzepatide is superior to placebo at improving osteoarthritis symptoms as measured by the mean change in WOMAC pain score at 72 weeks.
- H_1: Once-weekly, subcutaneous tirzepatide is superior to placebo at improving osteoarthritis symptoms as measured by the mean change in WOMAC function score at 72 weeks
- H_1: Once-weekly, subcutaneous tirzepatide is superior to placebo at improving osteoarthritis symptoms as measured by the mean change in WOMAC stiffness score at 72 weeks.
- H_1: Once-weekly, subcutaneous tirzepatide is superior to placebo at reducing the number of patients that progress to knee replacement or report being willing to undergo knee replacement in the target joint within 72 weeks.

8.2 Sample size determination

Approximately 352 participants will be randomised into the two equally sized study arms (i.e., 176 participants per arm). The sample size determination assumes a two-sided significance level of 0.05. The expected proportion of patients progressing to surgery within the primary follow up period is 85% in the tirzepatide arm, and 95% in the placebo arm and assumed that approximately 10% of participants randomized to each of the arms will drop out from the study. Given these assumptions, a sample 352 participants randomized to two equally sized groups provides 80% power to demonstrate the superiority of tirzepatide to placebo.

The sample size calculation is based on the most relevant data, primarily from recently completed randomized controlled trial (ABS study) conducted at one of the proposed study sites which demonstrated that when compared to lifestyle modification advice, surgical weight loss (via gastric banding) resulted in a 24.4 percentage point (95% CI, 9.0% to 39.8%) reduction in progression to surgery.[4] The sample size determination assumes that the proportion of patients in the control arm progressing to surgery and rates of loss to follow up in the proposed trial will mirror that in the control arm of the ABS study and of several other trials conducted in patients entering the orthopaedic surgery waiting list.[4,12,13] The assumed effect size employed for the sample size determination approximates the lower bound of the confidence intervals for the effect observed in the ABS trial.

8.3 General statistical considerations

All statistical analyses will be conducted in a blinded fashion, and any changes from the methods outlined in

the protocol will be described in the statistical analysis plan and final study report. Details on the planned analyses of long-term outcomes, and health economic analyses will be specified separately in the full statistical analysis plan.

Additional analyses of the trial data not described in the protocol or SAP may be conducted if appropriate, though the exploratory nature of all such analysis must be reported explicitly.

The full analysis set (FAS) will include all data obtained from all randomized participants during the planned treatment period, in the groups to which they were assigned, regardless of adherence to or discontinuation of the study drug. The main estimand of interest when comparing the efficacy and safety of tirzepatide to placebo will be a "treatment-regimen" estimand, which evaluates the effect of the treatment regardless of adherence to the study drug. The main analysis will assess outcomes measured at 72-weeks after randomization, in all randomized patients regardless of if they completed the planned course of treatment or discontinued the study drug early. As such, efficacy outcomes will be assessed according to the intention to treat (ITT) approach in the FAS.

All statistical tests will employ a two-side alpha of 0.05, unless otherwise stated. The results of all statistical analyses will be accompanied by two-sided 95% confidence intervals and p-values. Tirzepatide will be deemed superior to placebo when p-values are less than 0.05 and the treatment effect estimate favour the tirzepatide group.

8.4 Comparability of treatment groups.

Baseline demographic and clinical characteristics will be summarised for all randomized subjects according to their assigned treatment group.

Treatment compliance and participant disposition at the end of the trial will be described for all randomized subjects according to their assigned treatment group. This description will contain information on the number and proportion of patients in each treatment group that completed the study, discontinued the study, or were deemed non-compliant to the study drug. Reasons for early discontinuation of the study drug will also be reported.

8.5 Efficacy analysis

8.5.1 Primary analysis

The estimand of interest for our primary efficacy analysis when comparing the effect of tirzepatide to placebo will be the "treatment-regimen" estimand. It will compare the proportion of participants in each of the assigned treatment groups that progress to knee replacement within 72-weeks, regardless of adherence to the study drug and in the FAS. Relative risk and risk differences will be estimated via binomial regression.

8.5.2 Secondary analyses

All secondary and additional efficacy outcomes will be guided as the same "treatment-regimen" estimand as the primary analysis and will be assess assessed according to the intention to treat (ITT) approach in the FAS.

Linear mixed models using restricted maximum likelihood estimation will be used to estimate group differences at study completion for continuous outcomes, including changes in patient-reported outcome scores and in bodyweight. Secondary endpoints at 3-month intervals will be included as dependent variables in the model. The outcome measured at baseline, time, and study group will be included as fixed effects. An interaction between study group and time will be included in the model to estimate the between-group difference in outcomes at 3-month intervals. Repeated patient outcome measures will be treated as random effects in the model and an unstructured variance-covariance structure assumed.

A summary of the planned statistical analysis for all secondary efficacy outcomes is outlined below.

Objective	**Endpoint**	**Endpoint type**	**Estimand**	**Analysis set**	**Statistical Model**
Secondary	WOMAC pain change	Continuous	Primary	FAS	Linear mixed models
Secondary	WOMAC function change	Continuous	Primary	FAS	Linear mixed models
Secondary	WOMAC stiffness change	Continuous	Primary	FAS	Linear mixed models
Secondary	Willingness for surgery	Binary	Primary	FAS	Binomial regression
Secondary	Percentage change in body weight	Continuous	Primary	FAS	Linear mixed models
Secondary	≥5% reduction in body weight	Binary	Primary	FAS	Binomial regression
Secondary	≥10% reduction in body weight	Binary	Primary	FAS	Binomial regression
Secondary	≥20% reduction in body weight	Binary	Primary	FAS	Binomial regression
Secondary	SF-36 MCS change	Continuous	Primary	FAS	Linear mixed models
Secondary	SF-36 PCS change	Continuous	Primary	FAS	Linear mixed models
Secondary	PASE change	Continuous	Primary	FAS	Linear mixed models
Secondary	Non-opioid prescription analgesics	Binary	Primary	FAS	Binomial regression
Secondary	Opioid prescription analgesics	Binary	Primary	FAS	Binomial regression

Secondary	Opioid prescription analgesic dose	Continuous	Primary	FAS	Linear mixed models

8.6 Safety analyses

Analysis of all safety outcomes will be reported according to the intention to treat (ITT) approach in the FAS.

8.6.1 Adverse Events and Serious Adverse Events

To ensure comparability with prior phase III trials of tirzepatide, adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and reported with preferred terms. Counts and percentages of participants experiencing specific events will be reported for each treatment group. Counts and percentages of participants experiencing at least one AE, SAE, or AE requiring treatment discontinuation will also be presented separately for each treatment group.

No formal statistical tests will be carried on the number of AEs or SAEs.

8.7 Sensitivity analyses

Missing outcome data may be imputed using multiple imputation with chained equations. Further information on imputation procedures and sensitivity analyses will be prespecified in the statistical analysis plan.

8.8 Subgroup analyses

The following prespecified subgroup analyses will be presented:

- Sex (Male and Female)
- Baseline Body Mass Index (30 to <40, and ≥40 kg/m^2)
- Baseline Kellgren-Lawrence Grade (2, 3 or 4)
- Public vs private practice

The following outcome will be assessed in prespecified subgroup analysis:

- Proportion of patients who undergo knee replacement in the target joint within 72 weeks of randomization.
- A test of interaction will be used to assess subgroup effects.

8.9 Interim analyses

There are no planned interim analyses. Unplanned interim analyses may only be requested and conducted by the DMC, with blinding maintained if possible.

9. Ethical, Regulatory, and Study Oversight

9.1 Regulatory and ethical considerations

This study will be conducted in accordance with the NHMRC National Statement on Ethical Conduct in Human Research.[14] The protocol for this study will be submitted to all participating university and hospital

Human Research Ethics Committees (HREC) for assessment and approval. The conduct of this study will conform to the AHEC guidelines for human research and be performed in accordance with ICH GCP notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95). Participant recruitment will not commence until approval by the Institutional/Hospital HREC committee has been obtained. Any amendment to the protocol will be submitted to the relevant HREC. Implementation of any changes to trial delivery will only occur following HREC approval, unless changes are necessary to avoid an immediate hazard to participants. Investigators will be responsible for providing required updates on the progress of the study to the relevant ethics and governance committees at all studies sites.

9.2 Additional training requirements

All surgeons to be involved in the medication management of trial participants will have attended a training session on tirzepatide provided by an accredited endocrinologist or senior consultant physician familiar with the medication. Surgeons must also be provided a copy of the most up to date Investigator's Brochure (IB) and understand the role of the medical monitor (who is a senior consultant physician) assigned to the trial. Study sites are required to retain a register of evidence that each study surgeon has:

i. Attended the mandatory medication management session held by an accredited endocrinologist or senior consultant physician familiar with the medication.
ii. Received and read a copy of the Investigator's Brochure
iii. Have been provided a copy of the contact details and understand the role of the Medical Monitor.

All sites must undergo a site initiation visit by the independent trial monitor prior to commencing study recruitment. At the site initiation visit the independent trial monitor will record on the site initiation monitoring report that all steps outlined above have been completed, prior to recruitment commencement.

9.3 Informed consent process

Prior to obtaining consent, the site lead investigator or delegate will provide a verbal explanation of the study to the patient. The patient will then be given a copy of the Participant Information and Consent Form (PICF) and given an opportunity to read it and ask any questions of the site lead investigator or delegate. The patient will be encouraged to discuss their participation with their general practitioner and family members/significant others. Once the patient is satisfied with the information they have received, has had an opportunity to ask questions and obtain additional information, and the site lead investigator or delegate is satisfied that the patient truly understands the nature of the study, the patient will be asked to sign the consent form.

For participants who are unable to read the PICF, consent must take place in front of a witness and that witness must also be satisfied that the patient has a good understanding of the study. Patients will be advised that they

are free to refuse to participate in, or to withdraw from the study at any time. The medical care provided will not be affected by agreement or refusal to participate in this study. The original Consent Form for each subject will be stored in the Investigator's file and a copy of the consent form will be placed in the patient's medical record.

9.4 Data protection

Access to study data will be managed in line with the requirements of both local data protection laws and the requirements of relevant human research ethics committees. Identifiable information (e.g., names) will only be shared with external bodies (e.g., approved data linkage authorities) where necessary to achieve the trial's objectives, in a manner that is clearly outlined in the study consent documents. Participants will be informed that their medical records may be reviewed by site monitors, auditors, HREC members, and regulatory authorities as required by local regulations and legislation.

9.5 Data capture, confidentiality, and security

Data will be entered by study personnel using electronic case report form (eCRF) in a secure purpose-built online data capture platform, managed by Spiral Web Solutions Limited. Access will be limited to study personnel, and access will be manged via confidential log-in and password. The platform will include detailed audit logs and comply with the Food and Drug Administration's 21 CFR Part 11 Guidelines for Electronic Signatures (FDA 21 CFR Part 11). Investigators are responsible for maintaining separate source documents (e.g., laboratory test results, medical records, or clinical notes) for information entered into eCRFs. Paper-based assessments (e.g., study diaries) will be stored in hard copy format in the patient's file. paper source documents. All relevant source documents will be stored and maintained at investigator sites in a secure area within the hospital: either locked office in research department or another secure archive within the hospital or at a secure "off-site" storage facility

All identifiable study data will be kept strictly confidential. In addition to the study site research team, the sponsor's study monitor/s will have access to the source documents to validate the eCRF content throughout the study. The participant's medical records may also be accessed by authorised representatives of the sponsor, ethics committees and regulatory authorities for the purpose of audits and for verification of clinical trial procedures and data. At the completion of the study when the specified period of retention has finished, identifiable data will be disposed in a secure and safe manner in accordance with the Australian Code for the Responsible Conduct of Research, the University Records and Archives Management Policy, and the Victorian Public Records Act 1973. No information which could lead to the identification of a participant will be included in the dissemination of results.

For the purpose of health economic analysis and long-term follow-up, additional information may be linked with the data collected as a part of the trial. This may include data from the AOA NJRR, National Death Index, Medicare Benefits Schedule (MBS), Pharmaceutical Benefits Scheme (PBS), Victorian Admitted Episodes Dataset (VAED), Victorian Emergency Minimum Dataset (VEMD). Informed consent for data linkage with external datasets will be requested from all study participants, with the knowledge that this may require transfer

of patient details to an external body (e.g., Australian Institute of Health and Welfare, Centre for Victorian Data Linkage). All confidentially and security policies implemented by the custodians of these databases (e.g. the use of secure online research environments) will be documented and adhere to all study personnel.

9.6 Data quality assurance

To assure the quality of trial data, the coordinating principal investigator will:

- Provide training on trial protocols, procedures, and data collection to all study sites and personnel, including site leads and study coordinators,
- Design data collection procedures (e.g., eCRFs) to specifically highlight missing of implausible values during data collection,
- Visit sites periodically to review adherence to trial protocols, trial procedures, and data collection practices.

Site lead investigators are responsible for maintaining source documents (e.g., laboratory test results, medical records, or clinical notes) for information entered into eCRFs, which are to be made available to HRECs or regulatory bodies upon request.

9.7 Source documents

Site lead investigators are responsible for storing trial documents relevant to data management and maintaining a site-specific record of the location(s) of the site's trial documents.

Site lead investigators are responsible for maintaining accurate source documents. Source data will be attributable, legible (including any changes or corrections), contemporaneous, original, accurate, complete, consistent, enduring, and available. Changes to source data (hardcopy and electronic) must be readily tracible/auditable and must be explained where appropriate. Each site will maintain a source document plan that is approved by the trial steering committee throughout the trial.

9.8 Data monitoring committee

A draft charter for the data monitoring committee is outlined in the appendix (Section 10.3). The final DMC charter will be ratified by both the trial steering committee and DMC, prior to commencing enrolment.

9.9 Discontinuation of study or study sites.

The investigator or sponsor (with HREC approval) may discontinue or extend the study at any time. Investigators, sponsors, or HRECs may discontinue enrolment or follow up at individual sites if deemed necessary for any reasons (e.g., scientific, safety, or regulatory concerns) consistent with relevant laws or regulations.

9.10 Publication and translation strategy

Results will be published in timely fashion in a peer-reviewed journal, and summary results will be posted alongside the clinical trial registration. Study investigators will be potentially eligible for authorship on any publications arising from the STOP Knee-OA Trial. Criteria for authorship will be in keeping with the

International Committee of Medical Journal Editors. (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html).

Through their roles in policy development for pathways of care for osteoarthritis and knee replacement surgery within Governmental, consumer stakeholder and health care provider training frameworks, Investigators Dowsey and Choong will facilitate engagement and implementation of study outcomes. As an academic orthopaedic surgeon, past president of the Australian Orthopaedic Association (AOA), clinical champion and distinguished surgical leader, Investigator Choong will work on a communication strategy of trial outcomes with the AOA, to its members.

Should the STOP KNEE-OA trial demonstrate benefit to patients, the publication of robust trial evidence for the efficacy and cost-effectiveness of tirzepatide, will serve to support a submission to the Pharmaceutical Benefits Advisory Committee (PBAC) to recommend subsidising this medicine for people with obesity and knee osteoarthritis.

10. Appendix

10.1 Laboratory tests details

- Laboratory tests (outlined below) will be performed by each study sites central laboratory service.
- In the event that a sample is collected outside the central laboratory service and used to make a study intervention decision or treatment evaluation, these results should be entered onto the eCRF.
- Additional tests may be obtained in the event of anaphylaxis or systemic allergic or hypersensitivity reactions, as determined by the study physician or medical monitor.
- Additional tests may also be performed at any time during the study as deemed necessary by the study physician or medical monitor or if required by local regulations.

Full Blood Count (FBC)	• Haemoglobin (Hb) • White Blood Count (WBC) • Platelet Count (Plt) • Red Cell Count (RBC) • Haematocrit (HCT) • Mean Cell Volume - Red cell (MCV) • Mean Cell Haemoglobin (MCH)
Chemistry Panel	• Urea & Electrolytes (U&E) • Creatinine (Cr) • Urate (UA) • Phosphatase (Phos) • Total Calcium (Ca) • Albumin (Alb) • Total Protein (TP) • Total Bilirubin (T Bil) • Gamma-glutamyl transferase (GGT) • Alkaline phosphatase (ALP) • Alanine transaminase (ALT) • Aspartate aminotransferase (AST) • Lactate dehydrogenase (LDH) • Low Density Lipoprotein (LDL) • High Density Lipoprotein (HDL) • Triglycerides • Total Cholesterol (TC) • Glycated haemoglobin (HbA1c) • Fasting Blood Glucose • Magnesium

	• Thyroid Stimulating Hormone (TSH)
Hormones (Female)	• Human Chorionic Gonadotropin (hCG) • Follicle Stimulating Hormone (FSH)

10.2 Radiographic assessment

During screening, all potentially eligible participants must have the radiographic severity of osteoarthritis in the target joint assessed according to the Kellgren-Lawrence system. Grading will be conducted by accredited orthopaedic surgeon or radiologist who is not directly involved in the recruitment of the patient, using an appropriate x-ray of the target joint taken <180 days prior to the first screening visit. Appropriate x-rays include standard anteroposterior weightbearing (APWB), Rosenberg, or full length weightbearing (FLWB) views. When appropriate imaging taken during routine evaluation for entry onto the orthopaedic waitlist is not available, participants will undergo a standard anteroposterior weightbearing (APWB) x-ray of the target knee at the first screening visit.

10.3 Draft Data Monitoring Committee Charter

Trial Title: Effect of Subcutaneous Tirzepatide Once-weekly in Patients with Obesity and Knee Osteoarthritis (STOP KNEE-OA): A Randomized, Double-Blind, Placebo-Controlled Trial.

NCTID: NCT06191848

Trial Sponsor: The University of Melbourne

Data Monitoring Committee (DMC) Charter

Version 1.1 date 24 APRIL 2023
(Developed from DAMOCLES DMC Charter Template v1. February 2005)

Authorized by:

Name:	*Role:*
Signature:	*Date:*

Prepared by:

Name:	*Role:*
Signature:	*Date:*

1. INTRODUCTION

Name of trial	Effect of Subcutaneous Tirzepatide Once-weekly in Patients with Obesity and Knee Osteoarthritis (STOP KNEE-OA)
Sponsor	University of Melbourne
NCTID	NCT06191848
Objectives of trial, including interventions being investigated.	PRIMARY OBJECTIVE To determine if tirzepatide is superior to placebo at reducing the percentage of patients with knee osteoarthritis who progress to knee replacement. SECONDARY OBJECTIVES To determine if tirzepatide is superior to placebo at improving osteoarthritis symptoms, including: • Knee pain • Knee function • Knee stiffness • Reducing patient's willingness to undergo knee replacement. • Reducing bodyweight • Improving physical and mental health status • Increasing physical activity level • Reducing the use of prescription analgesics
Scope of Charter	The purpose of this document is to describe the membership, terms of reference, roles, responsibilities, authority, and decision making of the DMC for the STOP KNEE-OA trial. This includes the timing of meetings, methods of providing information to and from the DMC, frequency and format of meetings, statistical issues, and relationships with other committees.

2. ROLES AND RESPONSIBILITIES

Broad statement of the aims of the committee	To protect and serve STOP KNEE-OA trial patients regarding safety and to assist and advise the Principal Investigators (PIs) to protect the validity and credibility of the trial. To safeguard the interests of STOP KNEE-OA trial patients, assess the efficacy and safety of the intervention during the trial, and monitor the overall conduct of the STOP KNEE-OA trial.
Terms of reference	The DMC should receive and review the progress and accruing data of the STOP KNEE-OA trial and provide advice on the conduct of the trial to the Trial Steering Committee (TSC).

	The DMC should inform the Chair of the TSC if, in their view: (i) the results are likely to convince a broad range of clinicians, including those supporting the trial and the general clinical community, that one trial arm, or a subset of trial population, is clearly indicated or contraindicated, and there was a reasonable expectation that this new evidence would materially influence patient management: **or** (ii) it becomes evident that no clear outcome would be obtained.
Specific roles of the DMC	Conduct an interim review of the trial's progress including updated figures on recruitment, data quality, and main outcomes and safety data. • assess data quality, including completeness. • assess recruitment figures and losses to follow-up. • assess compliance with the protocol by participants and investigators. • assess evidence for treatment harm (e.g., SAEs, deaths) • decide whether to recommend that the trial continues or whether recruitment should be terminated. • monitor planned sample size assumptions. • monitor compliance with DMC recommendations. In addition, a DMC meeting might be triggered when: Two patients within a trial group experience any combination of: a serious adverse event (SAE) defined as possibly, probably or definitely related to the trial drug (i.e., it is a SAR), an adverse event that is severe and at least possibly related to the trial drug, or any of the objective stopping criteria detailed in the protocol (Any further single instances of the events outlined above for the same group will trigger a DMC safety review).
3. BEFORE OR EARLY IN THE TRIAL	
Whether the DMC will have input into the protocol	All potential DMC members should have sight of the protocol/outline before agreeing to join the committee. Before recruitment begins the trial will have undergone review by the funder/sponsor (e.g., peer review for public sector trials), and a human research ethics committee (HREC). Therefore, if a potential DMC member has major reservations about the trial (e.g., the protocol or the logistics) they should report these to the PI or trial coordinating team and may decide not to accept the invitation to join. DMC members should be independent and constructively critical of the ongoing trial, but also supportive of aims and methods of the trial.
Any specific regulatory issues	The DMC should be aware of any regulatory implications of their recommendations.

Whether members of the DMC will have a contract	DMC members will not be required to formally sign a contract but should formally register their assent to join the group by confirming (1) that they agree to be on the DMC and (2) that they agree with the contents of this Charter. Any competing interests should be declared at the same time. All members and observers attending any part of the meeting should sign a confidentiality agreement on the first occasion they attend all or part of a meeting.
4. COMPOSITION	
Membership and size of the DMC	Membership should consist of four members, who include at least one clinician experienced in the clinical area. Additional members experienced in clinical trials should reflect the other specialties involved in the trial. The members should not be involved with the trial in any other way or have some competing interest that could impact on the trial. Any competing interests, both real and potential, should be declared. A short competing interest form should be completed and returned by the DMC members to the trial coordinating team. The members of the DMC for this trial are: (1) TBA, Chair (2) TBA, Statistician (3) TBA, Physician (4) TBA, Surgeon
The Chair, how they are chosen and their role	The Chair should have previous experience of serving on DMCs and experience of chairing meetings and should be able to facilitate and summarise discussions. The Chair will be chosen by the TSC. The Chair is expected to facilitate and summarize discussions.
The responsibilities of the trial statistician	The trial statistician will have the overall responsibility for presenting the report to the DMC and will participate in DMC meetings, guiding the DMC through the report, and participating in DMC discussions.
The responsibilities of the trial coordinating team	The trial coordinator/project manager will prepare the report for the trial statistician. The trial coordinator/or project manager may attend open sessions of the meeting.
The responsibilities of the PI and other members of the TSC	The PI may be asked, and should be available, to attend open sessions of the DMC meeting. The other TSC members will not usually be expected to attend but can attend open sessions when necessary (See Section 6. Organization of DMC Meetings).
5. RELATIONSHIPS	
Relationships with PI(s), other trial committees (TSC), sponsor and regulatory bodies	A diagram is included in this charter (Figure 2) to illustrate the relationships between the trial committees and the sponsor.

Clarification of whether the DMC are advisory (make recommendations) or executive (make decisions)	The TSC will be responsible for the overall supervision of the trial progress, provide advice and make recommendations to the TSC. In addition, a DMC meeting may be triggered for safety reasons which are defined in the trial protocol and under 'specific roles of the DMC' in section 2. Under these circumstances the DMC will make executive decisions about the trial. If a DMC meeting is convened for reasons other than those described above, then their role will be in an advisory capacity to the TSC.
Payments to DMC members	Members should be reimbursed for travel and accommodation should in-person meetings be required.
The need for DMC members to disclose information about any competing interests	Competing interests should be disclosed. These are not restricted to financial matters – involvement in other trials or intellectual investment could be relevant.

6. ORGANISATION OF DMC MEETINGS

Expected frequency of DMC meetings	The exact frequency of meetings will depend upon any statistical plans specified and otherwise on trial events. The wishes of the DMC and needs of the trial coordinating team will be considered when planning each meeting. The DMC should meet at least yearly. An unplanned DMC meeting may be called by the Chair or requested by the TSC if there is an emergency concern on the safety of participants.
Whether meetings will be face- to-face or by teleconference	The first meeting should ideally be in-person to facilitate full discussion and allow members to get to know each other. Subsequent meetings will be by teleconference, unless in-person is requested.
How DMC meetings will be organized, especially regarding open and closed sessions, including who will be present in each session	DMC meetings may contain a mixture of open and closed sessions. <u>Closed sessions</u>: Only DMC members and others whom they specifically invite, e.g., trial statistician, are present in closed sessions. <u>Open sessions</u>: All those attending the closed session are joined by the PI(s), and sometimes also representatives of the sponsor, funder, or regulator, as relevant. <u>Proposed DMC meeting format</u>: (1) Open session: Introduction and any "open" parts of the report (2) Closed session: DMC discussion of "closed" parts of the report and, if necessary (3) Open session: Discussion with other attendees on any matters arising from the previous session(s) (4) Closed session: extra closed session

7. TRIAL DOCUMENTATION AND PROCEDURES TO ENSURE CONFIDENTIALITY AND PROPER COMMUNICATION

Intended content of material to be available in open sessions	Open sessions: Accumulating information relating to recruitment and data quality (e.g., data return rates, sample collection) will be presented. Pooled data will be presented and total numbers of events for the primary outcome measure and other outcome measures may be presented, at the discretion of the DMC.
Intended content of material to be available in closed sessions	Closed sessions: In addition to all the material available in the open session, the closed session material will include efficacy and safety data by treatment group.
Will the DMC be blinded to the treatment allocation	The DMC will not be blinded to the treatment allocation.
The people who will see the accumulating data and interim analysis	The confidential accumulating data and interim analysis by treatment allocation will be seen by the DMC members. DMC members do **not** have the right to share confidential information with anyone outside the DMC, including the PI.
Responsibility for identifying and circulating external evidence (e.g., from other trials/systematic reviews)	Identification and circulation of external evidence (e.g., from other trials/ systematic reviews) is not the responsibility of the DMC members. The PI, TSC and the trial coordinating team will collate any such information for presentation in an open session.
To whom the DMC will communicate the decisions/ recommendations that are reached	The DMC should report its decisions / recommendations in writing to the PI and TSC chair. This should be copied to the trial statistician and trial coordinator and if possible, should be sent via the trial coordinator in time for consideration at a TSC meeting where necessary. If the trial is to continue largely unchanged, then the report from the DMC should include a summary paragraph suitable for trial promotion purposes. In its communications, the DMC should be careful not to relay any unnecessary information to the TSC.
Whether reports to the DMC be available before the meeting or only at/during the meeting	For planned DMC meetings the DMC should receive the report at least 2 weeks before any meetings. For unplanned meetings it is recommended that all papers be brought to meetings by the trial coordinator; time would then be needed for DMC members to assimilate the data/report.
What will happen to the confidential papers after the meeting	The DMC members should store the papers safely after each meeting so they may check the next report against them. After the trial is reported, the DMC members should destroy all interim reports. A copy of all the reports will be held at the Department of Surgery, University of Melbourne

8. DECISION MAKING

What decisions/recommendations will be open to the DMC	Possible decisions/recommendations could include: • No action needed; trial continues as planned • Early stopping due, for example, to clear benefit or harm of a treatment, futility, or external evidence • Stopping recruitment within a subgroup • Extending recruitment or extending follow-up • Sanctioning and/or proposing protocol changes
The role of formal statistical methods, specifically which methods will be used and whether they will be used as guidelines or rules	The DMC should review and agree to any interim analysis plan. In addition, the DMC will meet to review the safety of the trial and will decide whether it is safe to progress the trial. The minimum dataset required for review BW trial groups will be: • All adverse events/adverse reactions • All relevant blood test results, and physical examination reports.
How decisions or recommendations will be reached within the DMC	The DMC chair should summarise discussions and encourage consensus; it may be best for the Chair to give their own opinion last. It is important that the implications (e.g., ethical, statistical, practical, financial) for the trial be considered before any recommendation is made.

9. REPORTING

To whom will the DMC report their recommendations/decisions, and in what form	By a letter to the PI and TSC chair delivered within 3 weeks for planned meetings and as promptly as possible following unplanned meetings. A copy of the DMC recommendations/ decisions will be stored in the trial master file.
Whether minutes of the meeting be made and, if so, by whom and where they will be kept	Minutes of the open session will be recorded by the Trials Coordinator. Minutes will be finalized upon signature of the chairperson and maintained by the sponsors in accordance with applicable statutory regulations. Minutes of the closed sessions will be recorded by a DMC designee separately from the minutes of the open session and stored securely by the sponsor. Closed session minutes, finalized by signature of the chairperson, will be maintained in confidence, and retained until discarded in accordance with applicable statutory regulation. Following each meeting, a report separate from the minutes of the open and closed sessions will be sent to the sponsor/TSC describing the DMC recommendations and rationale for such.
What will be done if there is disagreement between the DMC and the body to which it reports	If the DMC has serious problems or concerns with the TSC decision or vice versa a meeting of these groups should be held. The information to be shown would depend upon the action proposed and the DMC's concerns.

	Depending on the reason for the disagreement confidential data will often have to be revealed to all those attending such a meeting. The meeting should be chaired by an external expert who is not directly involved with the trial.
10. AFTER THE TRIAL	
Publication of results	At the end of the trial there may be a meeting to allow the DMC to discuss the final data with the key members of TSC and give advice about data interpretation.
The information about the DMC that will be included in published trial reports	DMC members should be named, and their affiliations listed in the main report, unless they explicitly request otherwise. A summary of the timings and conclusions of DMC meetings should be included in the body of this paper.
Whether the DMC will have the opportunity to approve publications	The DMC will be given the opportunity to read and comment on publications before submission.
Any constraints on DMC members divulging information after the trial has been published	The DMC may discuss their involvement in the trial 12 months after the primary trial results have been published.

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