A Study of Cardiovascular Events iN Diabetes – PLUS (ASCEND PLUS)
A streamlined trial of oral semaglutide for prevention of cardiovascular events in people with type 2 diabetes

Does treatment with oral semaglutide prevent major adverse cardiovascular events in people with type 2 diabetes and no prior myocardial infarction or stroke?

Individuals with type 2 diabetes mellitus (T2DM) are at twice the risk of suffering cardiovascular events and high risk of premature death compared to those without diabetes. They are also at risk of microvascular complications (including chronic kidney disease and lower extremity amputation) and have an increased long-term risk of dementia. Large randomised trials conducted in participants with T2DM with, or at high risk of, cardiovascular disease have established that treatment with injectable glucagon-like peptide-1 (GLP-1) receptor agonists (RA) reduces cardiovascular events compared to placebo. These medications also improve glycaemic control, reduce weight and blood pressure, and appear likely to reduce progressive chronic kidney disease and metabolic complications of T2DM such as non-alcoholic steatohepatitis. However, such treatments require regular injections and uptake remains low in the United Kingdom and globally.

Randomised trials of GLP-1 RAs have been conducted in individuals with T2DM at very high cardiovascular risk but evidence for cardiovascular disease prevention in the majority with T2DM who are at moderate or high risk is limited. The identification of safe, cost-effective and scalable therapies that reduce cardiovascular, and microvascular, complications of diabetes would support their earlier and widespread use, and could yield substantial public health gains. Oral semaglutide is the first oral GLP-1 receptor agonist. Its effects on glycaemia, weight and blood pressure are comparable to injectable GLP-1 receptor agonists. Large-scale trials are now needed to determine whether oral semaglutide should be routinely used in people with T2DM at moderate or high cardiovascular risk.

A streamlined trial conducted in the UK

ASCEND PLUS is a randomised, double-blind, parallel-group, placebo-controlled event driven trial designed to test the hypothesis that oral semaglutide reduces cardiovascular events and other complications of diabetes in people with T2DM without a prior myocardial infarction or stroke. The study will use streamlined methodology to randomise approximately 20,000 people with T2DM in the UK and follow them during a scheduled treatment period with a median duration of approximately 5 years.

The study was initiated and designed by the Clinical Trial Service Unit (CTSU) at the University of Oxford, the trial sponsor. It was developed with contributions from Novo Nordisk, and is funded by Novo Nordisk. It will be coordinated by CTSU, which will be responsible for its conduct, analysis and reporting. The study design is innovative and streamlined: participants will be identified from centrally held routinely collected healthcare datasets and invited to join the trial. There will be no physical sites, and all interactions with participants will be conducted directly using innovative patient-centred web-based technology, supplemented by telephone, video call contact and mailed letters. Study treatment will be mailed to participants. Given that detailed information about tolerability, non-serious adverse events and laboratory data have been collected in previous oral semaglutide trials, the trial will focus on collecting serious adverse events and study outcomes relevant to patients with T2DM by regular linkage to National Health Service health records both during the scheduled treatment period and for the subsequent 20 years' long-term follow-up after the scheduled treatment period. With comprehensive data collection and large sample size, this trial will produce a reliable assessment of the medium and long-term effects of adding oral semaglutide therapy to standard of care in a broad population of people with T2DM.

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Version History

Version	Date	Summary
0.1	22 July 2020	Draft version
1.0	9 April 2021	Version included in the funding agreement
1.1	16 June 2021	Update secondary outcome and tertiary outcomes
1.2	9 November 2021	Section 1.1.2 updated with recent trial. Sections 2.7.2 and 6.1.5 added to describe collaboration with NIHR and NHS Sections 3 and 3.3.1 updated in line with revised practical procedures Section 3.1.2 eligibility minor changes Section 3.6.1 updates with patient-reported-outcomes Section 6.4.2 DMC members added
1.3	3 January 2022	Clarification to wording about the scheduled treatment period and study sites throughout Section 2.5.3 added describing the preparation of the DSUR Section 2.7.3.3 added relating to serious breach reporting Section 2.7.3.4 added describing access to data for audit Section 3.7 updated to indicate period off study treatment which would require dose escalation
1.4	18 January 2022	Minor edits during sponsor review
1.5	1 February 2022	Minor edits after further Steering Committee review Removal of Section 6.4.2 (DMC membership), this is included in the DMC charter Section 3.5.2: clarification regarding minimised randomisation Section 4.3: clarification regarding application of participant identifier ancillary label at the point of mailing study treatment
1.6	16 February 2022	Section 2.5.1: remove wording about transition from manual coding to algorithmic coding of NHS data (this will be covered in future amendment) Section 2.7.4: wording added regarding study database Section 3.6.1: wording removed about plans for regular follow up with relative/carer
1.7	2 May 2022	List of abbreviations added; Section 2.5: advice regarding pregnancy now removed given that pregnancy and breastfeeding are now listed as exclusion criteria; Section 2.5.2.5: cancer not exempt from expedited reporting; Section 3.1.2: exclusion criteria include GLP1-RA use before randomisation (not only at screening), breastfeeding / pregnancy / planning pregnancy, unwillingness to undertake regular TFT monitoring if on thyroxine, definitions for hypoglycaemia added; Section 3.8.1: clarifications added regarding prohibited medications, contraindicated clinical conditions and medications; Section 4.4.3: details added regarding thyroxine treatment Section 3.3.2: participant will be asked to sign mailed consent copy and return to the CCO by post

1.8	20 Sep 2022	REC reference, ISRCTN number, CT.gov number included Section 2.5.1: clarification regarding NHS datasets for linkage Section 2.5.2: correction of SOP name Section 2.5.2.1: clarification regarding which AEs can/will be recorded Sections 2.5.2.2 and 3 and 3.6.1: clarification that participants will be asked about a subset of study outcomes Section 2.5.2.5: clarification regarding RSI (SmPC) Sections 3.2 and 6.1.4: update to recruitment which will now not require Oxford to receive any data without participant's agreement Section 3.6.1 and 6.3: change from SF-12 to VR-12 questionnaire during follow up Section 3.9: clarification regarding process for confirming study outcomes Section 4.4: reference to the EU SmPC rather than the UK Section 6.2: estimand wording clarified due to non-collapsibility of adjusted hazard ratio Section 6.3: correction to footnote (PAID at 3 years) Section 6.4: Update to Steering Committee membership and inclusion of Clinical Coordinator
2.0	12 Aug 2024	Addition of Section 2.3.1.10 regarding analysis of sub-studies Section 2.5.2.5: clarification regarding the reference safety information used to determine expectedness Section 2.7.2: change to allow allied health professionals and other suitably trained staff to undertake study assessments and respond to participants questions about the trial Change 'research nurse' to 'research coordinator' throughout Change NHS Digital to NHS England throughout following merger of the two organisations Section 3.2: changes relating to the invitation letter sub-study Section 3.6.1 and Section 6.3 Appendix 3: changes in relation to the timing of the VR-12 and PAID questionnaires Updated to section 4.4.3 regarding possible interaction between oral semaglutide and acenocoumarol Section 6.4.1: changes relating to the Novo Nordisk Steering Committee members Addition of Section 6.5: Appendix 5 details of approved sub-studies
3.0	06 Oct 2025	Section 2.3.1.3 Removal of the outcome 'total MACE events' from the tertiary assessments Section 2.5.2.2: If SAE reported which reporter (non-professional) considers related to study treatment and the CCO clinician does not, then seek opinion of treating doctor Section 3.3.2: refer to e-Consent evaluation Addition of Section 6.6.1 describing the ethics of e-Consent evaluation Section 6.4.1: update title of investigator, remove member and add members

Trial synopsis

Trial title	A Study of Cardiovascular Events iN Diabetes PLUS
Short title	ASCEND PLUS
Lay description	This trial is called ASCEND PLUS. It is testing whether, for people with diabetes who have not previously had a heart attack or stroke, regularly taking a tablet called semaglutide can safely help to reduce heart attacks, strokes, mini-strokes, the need for any procedures to unblock or bypass an artery to their heart, and the chance of dying because of vascular problems.
Clinical phase	IV
Trial design	Randomised double-blind placebo-controlled trial
Sponsor	The University of Oxford will act as the sponsor of the trial
Protocol number	CTSU_ASCEND-PLUS
IRAS number	1004252
REC number	22/SC/0116
ISRCTN number	ISRCTN76193287
NCT number	NCT05441267
EudraCT number	2021-003792-33
Eligibility of trial participants	Key eligibility criteria are: 1. Age ≥55 years 2. Type 2 diabetes mellitus 3. No self-reported history of myocardial infarction or stroke 4. Absence of any other exclusion criteria (as described in Section 3.1.2)
Planned sample size	Approximately 20,000 participants
Investigational medicinal product	Oral semaglutide
Formulation, dose, route of administration	*Active run-in*: Run-in phase consisting of 4-weeks of active 3mg oral semaglutide followed by 4 to 8-weeks of active 7mg oral semaglutide; taken as one tablet daily starting with 3mg bottle, then 7mg bottles. *From randomisation*: 24-week packs of oral semaglutide 14mg or placebo tablets sent out regularly (double-blind); taken as one tablet daily. There will be an opportunity to reduce dose to 7mg or matching placebo; taken as one tablet daily. When a participant restarts study treatment after a prolonged period off treatment they will restart study treatment with 4-weeks of 3mg/placebo tablets and then 4 to 8-week 7mg/placebo tablets after which they will revert to 24-week packs of 14mg/placebo or 7mg/placebo. Study treatment will be mailed out.
Treatment duration	The scheduled treatment period, during which participants are requested to take the study treatment and complete follow-up assessments, is anticipated to continue until at least 1600 participants have experienced a primary outcome following randomisation. This is expected to occur at a median of approximately 5 years after randomisation.
Primary outcome	The expanded composite of major adverse cardiovascular events (MACE+), defined as: • Death from cardiovascular disease • Non-fatal myocardial infarction • Non-fatal stroke • Transient ischaemic attack • Coronary revascularisation
Secondary outcome	The composite of major cardiovascular events (MACE): • Death from cardiovascular disease • Non-fatal myocardial infarction • Non-fatal stroke

List of abbreviations

ACS	Acute coronary syndrome
AE	Adverse event
ASCEND	A Study of Cardiovascular Events iN Diabetes
ASCEND PLUS	A Study of Cardiovascular Events iN Diabetes – PLUS
AUC	Area under the curve
CCO	Central Coordinating Office
CI	Confidence intervals
CKD	Chronic kidney disease
Cmax	Maximum concentration
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTSU	Clinical Trial Service Unit and Epidemiological Studies Unit
CVD	Cardiovascular disease
CVOT	Cardiovascular outcome trial
DMC	Data Monitoring Committee
DSUR	Data Safety Update Report
eGFR	Estimate glomerular filtration rate
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP-1	Glucagon-like peptide 1
GLP1-RA	Glucagon-like peptide 1 receptor agonists
GMP	Good Manufacturing Practice
GP	General Practitioner
HbA1c	Glycated haemoglobin A1c
HDPE	High density poly ethylene
HR	Hazard ratio
ICH	International Conference on Harmonisation
IMP	Investigational medicinal product
INR	International normalised ratio
IT	Information technology
MACE	Major adverse cardiovascular event

MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MODY	Maturity onset diabetes of the young
NASH	Non-alcoholic steatohepatitis
NHS	National Health Service
NIHR	National Institute for Health and Care Research
NYHA	New York Heart Association
PAID	Problem Areas In Diabetes
QP	Qualified Person
RA	Receptor agonist
REC	Research Ethics Committee
RSI	Reference Safety Information
SAR	Serious Adverse Reaction
SGLT2	Sodium-glucose co-transporter 2
SmPC	Summary of Product Characteristics
SMS	Short Message Service
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
T2DM	Type 2 diabetes mellitus
TIA	Transient ischaemic attack
UACR	Urine albumin creatinine ratio
UK	United Kingdom
VR-12	Veterans RAND 12 Item Health Survey (VR-12)

Table of contents

1 BACKGROUND AND RATIONALE

1.1 DOES TREATMENT WITH THE GLP-1 RECEPTOR AGONIST, ORAL SEMAGLUTIDE, REDUCE CARDIOVASCULAR EVENTS AND OTHER COMPLICATIONS AMONG PEOPLE WITH TYPE 2 DIABETES WHO HAVE NOT PREVIOUSLY SUFFERED A MYOCARDIAL INFARCTION OR STROKE?

1.1.1 Type 2 diabetes mellitus is associated with elevated risks of cardiovascular disease and other conditions

Globally, about 1 in 11 adults has diabetes, and 90% of individuals with diabetes have type 2 diabetes (T2DM) [1]. Pooled data from observational studies, predominantly conducted in Europe and North America, show that the presence of diabetes approximately doubles the risk of vascular outcomes such as coronary heart disease, ischaemic stroke, and cardiovascular death while more extreme risks are observed in regions where medications to control glycaemia are not widely available [2, 3]. Although the risk of death from cardiovascular disease in the United States (US) and Europe has fallen over the last 20 years in people with and without diabetes [4], those with diabetes remain at substantially higher risk [5] and the increasing prevalence of T2DM suggests that the total global burden of cardiovascular disease resulting from diabetes is likely to increase [6].

T2DM also exposes affected individuals, especially those with longstanding diabetes and poor glycaemic control, to the risk of microvascular complications including chronic kidney disease (CKD), peripheral neuropathy and retinopathy. Diabetes remains the most common cause of CKD [7] and is an increasing cause of visual loss worldwide [8]. Diabetic peripheral neuropathy is associated with pain, impaired mobility and foot ulceration, and is a leading cause of lower limb amputation [9].

Individuals with T2DM are well known to have higher body weight than those without diabetes (for example, 4-5kg/m^2 heavier in the UK Biobank study [10]) and, consequently, are more likely to have associated cardiovascular risk factors like hypertension and to develop metabolic complications such as progressive non-alcoholic fatty liver disease [11]. Diabetes and obesity are both associated with increased risk of dementia, particularly vascular dementia [12, 13].

1.1.2 GLP-1 receptor agonist therapy and its effects on the risk of cardiovascular events, decline in kidney function and metabolic complications

Glucagon-like peptide 1 (GLP-1) is released by entero-endocrine cells in the intestine after food intake and augments insulin secretion and modulates glucagon secretion [14]. Both genetic [15] and clinical trial data support a protective role for GLP-1 with regard to cardiovascular disease. Nine placebo-controlled cardiovascular outcome trials of patients with T2DM and prior cardiovascular disease or at substantially increased cardiovascular risk have assessed GLP-1 receptor agonists (RA) to date (Table 1) [16-24].

Table 1: Completed trials assessing the effect of GLP-1 RAs on cardiovascular events

Trial, year reported	Agent	N	Population (all with T2DM)	Ave. age (years)	Prior CVD	Follow up duration (years)	Placebo run-in	Discontinued(active vs control)	Outcomes (active vs placebo) †	Hazard ratio (95% confidence interval)
ELIXA, 2015 [16]	Lixisenatide	6068	Recent ACS	60	100%	2.1	1 week	28 vs 24%*	406 vs 399	1.02 (0.89-1.17)
LEADER, 2016 [17]	Liraglutide	9340	CVD or ↑ risk	64	81%	3.8	2 week	15 vs 13%‡	608 vs 694	0.87 (0.78-0.97)
SUSTAIN-6, 2016 [18]	Semaglutide	3297	CVD or ↑ risk	64	82%	2.1	none	13% vs 10%‡	108 vs 146	0.74 (0.58-0.95)
EXSCEL, 2017 [19]	Exenatide	14752	CVD or ↑ risk	62	73%	3.2	none	43 vs 45%*	839 vs 905	0.91 (0.83-1.00)

HARMONY, 2018 [20]	Albiglutide	9463	CVD	64	100%	1.6	none	25 vs 28%*	338 vs 428	0.87 (0.68-0.90)
PIONEER-6, 2019 [21]	Oral semaglutide	3183	CVD or ↑ risk	66	85%	1.3	none	15 vs 10%*	61 vs 76	0.79 (0.57-1.11)
REWIND, 2019 [22]	Dulaglutide	9901	CVD or ↑ risk	66	31%	5.4	3 week	18 vs 17%‡	564 vs 663	0.88 (0.79-0.99)
AMPLITUDE-O, 2021 [23]	Efpeglenatide	4076	CVD or ↑ risk	65	90%	1.8	none	11% vs 9%§	125 vs 189	0.73 (0.58-0.92)
FREEDOM CVO [24]	Exenatide	4156	CVD or ↑ risk	63	76%	1.3	none	18% vs 14%*	85 vs 69	1.24 (0.90-1.70)

ACS, acute coronary syndrome; CVD, cardiovascular disease; N, sample size; Ave, average
† vascular death, non-fatal myocardial infarction or non-fatal stroke except ELIXA which also included unstable angina and AMPLITUDE-O which also included deaths of undetermined cause; *end of trial, ‡mean, §non-exposure in follow-up

Together these trials included 64,236 participants, the vast majority at very high cardiovascular risk (due to established cardiovascular disease or multiple risk factors). Tabular meta-analyses demonstrated reductions in major cardiovascular events (hazard ratio [HR] 0.87; 95% confidence interval [CI] 0.81-0.94) and all-cause mortality (HR 0.89; 95% CI 0.83-0.95) in analyses of the nine trials [25], and reductions in stroke (HR 0.83; 95% CI 0.76-0.92), myocardial infarction (HR 0.90; 95% CI 0.83-0.98) and death from cardiovascular disease (HR 0.87; 95% CI 0.80-0.94) in analyses of eight trials [26]. There was no increase in severe hypoglycaemia (HR 0.90; 95% CI 0.74-1.10) and a composite renal outcome was also reduced (six trials [n=44,378]; HR 0.79; 95% CI 0.73-0.87) [26]. The REWIND trial is notable in that 70% of participants did not have established cardiovascular disease (they did have at least two risk factors from use of tobacco, hypertension, dyslipidaemia, abdominal obesity). Some of these trials were limited by relatively short follow-up duration, lack of a run-in and poor adherence to treatment. Consequently, the relative effects of GLP-1 RA therapy may have been underestimated by these trials. In addition, while there is no statistically significant heterogeneity across the trials regarding the effects of the various GLP-1 RAs on cardiovascular outcomes [26], it has been suggested that more potent GLP-1 RAs, like semaglutide, may offer greater cardiovascular benefit than weaker or shorter acting agents [27].

The mechanism for the observed reduction in cardiovascular risk is unclear. GLP-1 RA therapy reduces blood pressure, weight and measures of glycaemia compared to placebo [28]. Improved glycaemic control is unlikely to fully explain the reduction in cardiovascular events, suggesting that GLP-1 RA therapy may offer cardiovascular benefit regardless of baseline HbA1c. Although improved glycaemic control may account for the observed reduction in adverse renal outcomes, direct effects of GLP-1 in the kidney have been postulated [29].

Completed placebo-controlled cardiovascular outcome trials of semaglutide have been relatively small, but their results are consistent with at least the same cardiovascular benefit as observed in trials of other GLP-1 RAs (Table 1).

1.1.3 Rationale for a large trial of oral semaglutide therapy in participants with T2DM and without a prior myocardial infarction or stroke

Following the publication of guidance by the US Food and Drug Administration (FDA) in 2008 regarding the need to establish the cardiovascular safety of glucose-lowering therapies, many cardiovascular outcome trials (CVOTs) have been conducted to evaluate the effects of dipeptidyl peptidase 4 inhibitors, sodium-glucose co-transporter 2 (SGLT2) inhibitors and GLP-1 RAs. However, criticisms of some of these CVOTs are that they were of relatively short duration as event-driven studies, recruiting very high–risk populations unrepresentative of the general population prescribed these agents [30]. While it is reasonable to extrapolate evidence of cardiovascular *safety* from these studies to the far greater numbers of patients with T2DM who are at moderate to high risk of cardiovascular

events, similar extrapolations for cardiovascular *efficacy* may not be valid. For example, pooled data from placebo-controlled trials of SGLT2 inhibitors show clear reductions in atherosclerotic cardiovascular events in patients with established cardiovascular disease but it is currently unclear if there is any such effect in high-risk primary prevention patients [31]. The FDA has recently announced new draft guidance to consider broader evaluations for T2DM [32], and pragmatic CVOTs have been suggested to overcome many of the criticisms of the traditional CVOTs.

This is reflected in recent T2DM guidelines that give clear guidance regarding the treatment of those with established cardiovascular disease or at very high risk, but not in those at moderate to high risk [33]. For patients in the latter group, metformin is typically recommended as first-line monotherapy, regardless of HbA1c, followed by a choice of multiple different options for combination therapy if HbA1c remains above a certain level. In the UK and globally, the majority of patients receive metformin monotherapy with second line treatment initiated only when HbA1c is well above target (often 8-9%) [34, 35]. This therapeutic inertia may, in part, be related to concerns raised by previous trials demonstrating excess mortality with intensive glycaemic control, using predominantly sulphonylurea and insulin treatment, among people with T2DM who have, or are at very high risk of, cardiovascular disease [36].

Reliable randomised evidence showing beneficial effects of a glucose-lowering therapy, without appreciable hazard, on cardiovascular, microvascular and metabolic complications in a broad range of T2DM patients (who are at high lifetime risk for such complications), would support earlier and more widespread use of such a therapy. With advantageous effects on cardiovascular events, glycaemic control, weight and the avoidance of hypoglycaemia, GLP-1 RA therapy is an appealing treatment for patients with T2DM but uptake in clinical practice remains low. In the United Kingdom (UK), for example, injectable GLP-1 RA therapy is typically reserved for third or fourth line combination glucose-lowering therapy, and is prescribed only once for every 15 metformin prescriptions (Figure 1). This may reflect challenges in providing and managing an injectable therapy at scale and may also reflect the lack of evidence for cardiovascular benefits in those without established cardiovascular disease.

Oral semaglutide is the first oral GLP-1 RA approved by the FDA and European Medicines Agency for glycaemic control in patients with T2DM. Oral semaglutide (14mg daily) is at least as effective as injectable liraglutide (1.8mg daily) and comparable to injectable semaglutide (0.5-1mg weekly) at reducing HbA1c, weight and blood pressure [37, 38]. By avoiding the need for self-injection, oral semaglutide has the potential for widespread use in patients with T2DM but reliable evidence on its long-term cardiovascular efficacy and safety, in particular among people without prior cardiovascular disease, is needed.

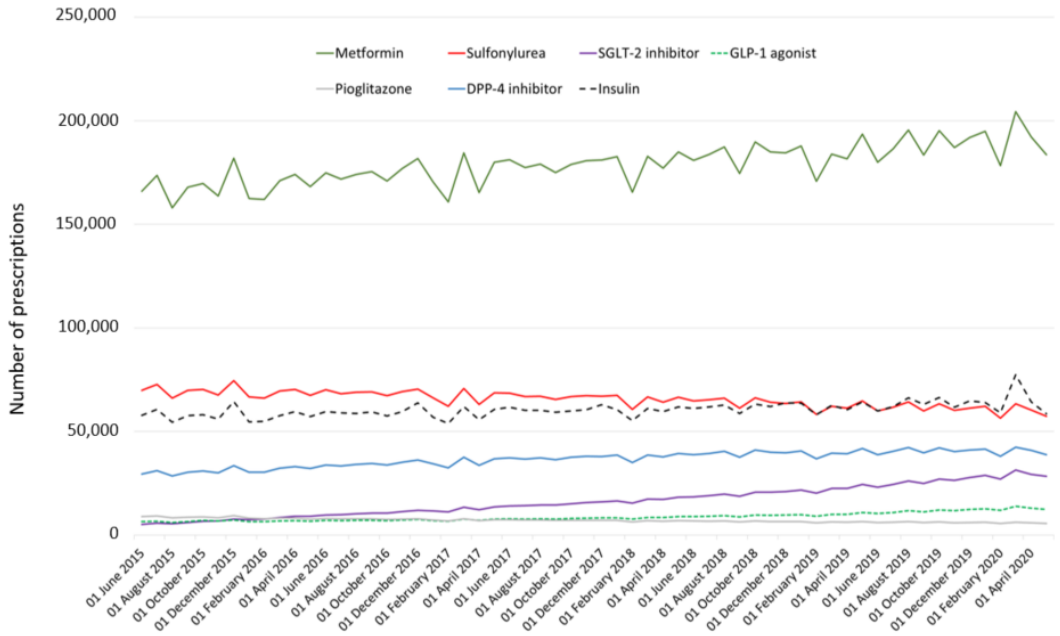

Figure 1. *Prescriptions for hypoglycaemic medication in England between 2015 and 2020 (data available at www.openprescribing.net; does not include combination preparations)*

1.2 A STREAMLINED TRIAL

In order to reliably answer whether oral semaglutide reduces cardiovascular and other complications in patients with T2DM, the ASCEND PLUS trial needs to be large and highly streamlined. The trial will be coordinated using a similar approach to our successful mail-based ASCEND trial, which recruited 15,000 people with diabetes but no prior atherosclerotic vascular disease, in the UK [39, 40]. ASCEND PLUS will be run entirely in the UK and will have no physical sites, with all activities coordinated from the Central Coordinating Office (CCO) based at the Clinical Trial Service Unit (CTSU), University of Oxford. Potential participants will be identified from centrally held, routinely collected healthcare datasets (with appropriate privacy approvals) and invited to join the trial. Approximately 20,000 participants will be recruited and followed up by online questionnaires (web-based and app technology), supported by telephone/video call contact from the trial team and mailed letters where necessary. Study treatment will be posted to participants. The trial incorporates an active pre-randomisation run-in phase to maximize the likelihood that randomised participants will remain adherent to the study treatment.

Assessments will be simple and utilise secure web-based IT software which will be used to electronically record informed consent and determine eligibility. Wherever possible, information (including trial outcomes) will be collected from centrally held routinely collected health data, both during the scheduled treatment period and for the subsequent 20 years. With comprehensive data collection and large sample size, this trial will produce a reliable assessment of the medium and long-term effects of adding oral semaglutide therapy to standard of care in a broad population with T2DM.

2 PLAN OF INVESTIGATION

2.1 STUDY AIMS

The ASCEND PLUS trial aims to provide evidence about both the efficacy and safety of prolonged treatment with oral semaglutide. The hypothesis of the ASCEND PLUS trial is that treatment with oral semaglutide reduces cardiovascular events and other complications of diabetes in individuals aged at least 55 years, with T2DM, without a history of a myocardial infarction or stroke, and without any upper or lower HbA1c threshold. The trial will primarily use streamlined web- and mail-based methodology to randomise approximately 20,000 people with T2DM and no history of myocardial infarction or stroke, all recruited within the UK. Pre-specified outcomes for the trial are described in Section 2.3.1. Linkage with routine National Health Service (NHS) healthcare datasets and national registries will allow high quality data collection and complete follow-up without any local site visits. Ongoing collection of health data after the end of the scheduled treatment period will also allow reliable assessment of the long-term effects of oral semaglutide.

2.2 TREATMENT COMPARISONS

2.2.1 Run-in period prior to randomisation

The study includes an ascending dose active run-in period. The intention of this phase is to identify participants who are less likely to remain adherent to study treatment during the randomised phase and to allow patients' General Practitioners (GPs) to raise any concerns regarding their patient joining the trial. An ascending dose active run-in is preferred to a placebo run-in given that gastrointestinal side-effects (such as nausea) are common, but often transient, on GLP-1 RA therapy and typically occur during treatment initiation and dose escalation.

2.2.2 Randomisation to oral semaglutide versus placebo

After successfully reaching treatment with 7mg oral semaglutide during run-in, eligible and consenting individuals who confirm that they wish to fully enter the trial will be allocated oral semaglutide (14mg starting dose) or placebo using a minimised randomisation program on the trial IT systems (see Section 3.5.2).

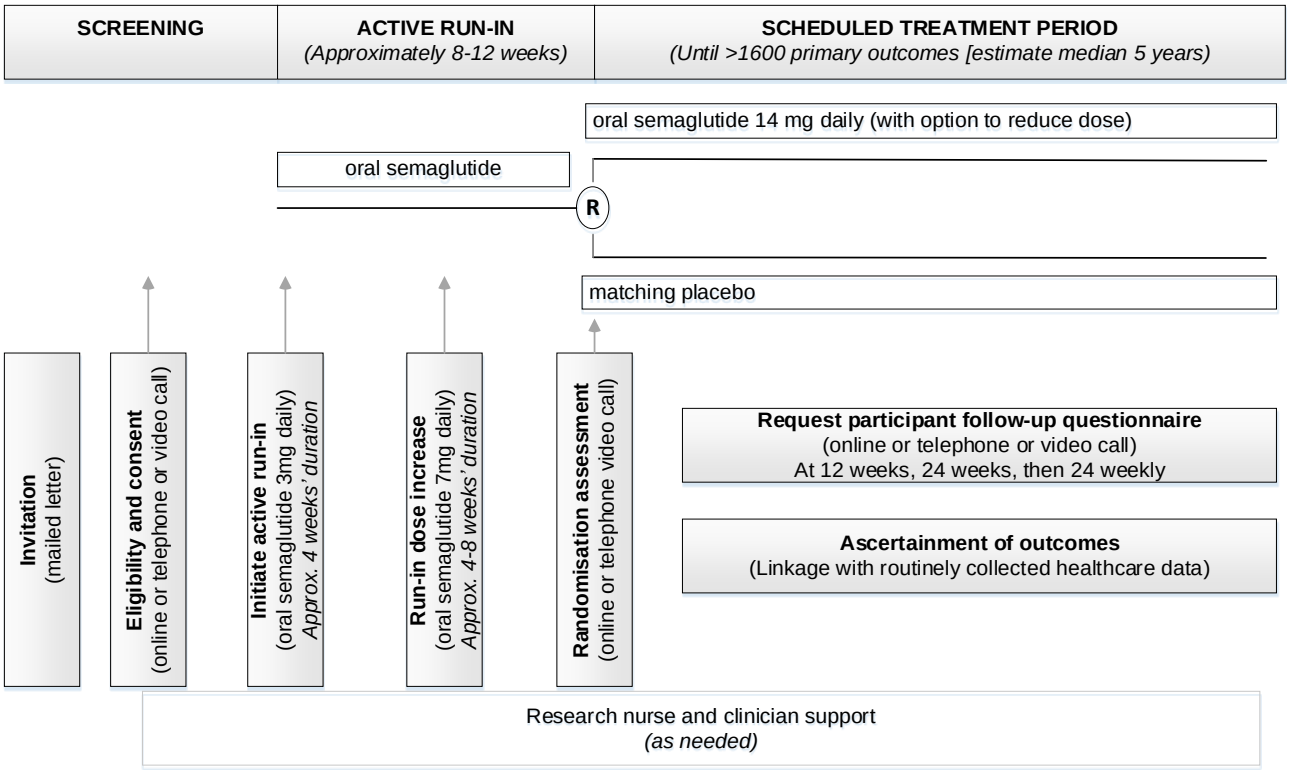

Figure 2. *Outline of run-in, randomisation and follow-up schedule*

2.3 STATISTICAL ANALYSIS PLAN

2.3.1 Primary and subsidiary assessments

2.3.1.1 Primary assessment

The primary assessment will involve a comparison among all randomised participants of the effects of allocation to oral semaglutide versus placebo during the scheduled treatment period on time to first occurrence of the primary outcome. The primary outcome is the expanded composite of major adverse cardiovascular events (MACE+, defined as death from cardiovascular disease, non-fatal myocardial infarction, non-fatal stroke, transient ischaemic attack [TIA] and coronary revascularisation) during the scheduled treatment period. Attributes of the primary estimand are provided in Section 6.2.1.

2.3.1.2 Secondary assessment

The secondary assessment will involve a comparison among all randomised participants of the effects of allocation to oral semaglutide versus placebo during the scheduled treatment period on time to first occurrence of the secondary outcome. The secondary outcome is the composite of major adverse cardiovascular events (MACE, defined as death from cardiovascular disease, non-fatal myocardial infarction, non-fatal stroke). Attributes of the secondary estimand are provided in Section 6.2.2.

2.3.1.3 Tertiary assessments

Tertiary assessments will involve comparisons among all randomised participants of the effects of allocation to oral semaglutide versus placebo during the scheduled treatment period on time to first occurrence (unless otherwise indicated) of the following outcomes, with due allowance in their interpretation for multiple comparisons:

(i) Components of the primary outcome (namely death from cardiovascular disease; non-fatal myocardial infarction; non-fatal stroke; TIA; coronary revascularisation)

(ii) Major adverse limb events (the composite of hospitalisation for acute or chronic lower limb ischaemia, non-traumatic lower limb amputation and lower limb arterial revascularisation)
(iii) Kidney function decline (the composite of sustained[a] ≥40% estimated glomerular filtration rate [eGFR] decline[b], sustained[a] eGFR <15 mL/min/1.73m^2, maintenance dialysis[c], kidney transplant or death from kidney disease)
(iv) Commencement of insulin therapy (only in patients not on insulin at baseline)

Attributes of the tertiary estimands are provided in Section 6.2.3.

2.3.1.4 Exploratory assessments

Exploratory assessments will involve comparisons among all randomised participants of the effects of allocation to oral semaglutide versus placebo during the scheduled treatment period on time to first occurrence (unless otherwise indicated) of the following outcomes, with due allowance in their interpretation for multiple comparisons:

(i) Chronic disease related to excess weight (among those without evidence of the condition prior to randomisation) defined as the composite of non-alcoholic steatohepatitis (NASH), obstructive sleep apnoea, knee replacement surgery
(ii) Microvascular disease defined as the composite of kidney function decline, hospitalisation for diabetic foot, and progression of diabetic retinopathy (progression to referable diabetic retinopathy or maculopathy, or the need for treatment with retinal laser, vitrectomy or intravitreal injection)
(iii) Progression to macroalbuminuria[a] (among those without evidence of macroalbuminuria prior to screening)
(iv) Slope of eGFR over time**Error! Bookmark not defined.**
(v) Dementia or cognitive impairment
(vi) Mortality from all causes combined and, separately, within particular categories of causes, including cardiovascular death, non-cardiovascular medical death, undetermined causes and external causes of death
(vii) The composite of severe hypoglycaemia (requiring urgent bystander intervention [as reported to the CCO] or resulting in attendance at Accident and Emergency) and Serious Adverse Events (SAE) of hypoglycaemia

2.3.1.5 Clinical safety assessments

The schedule of planned assessments is provided in Section 6.3. SAEs and outcomes will be captured in the study database to be used for safety assessments. Safety assessments will involve intention-to-treat comparisons among all randomised participants of the effects of allocation to oral semaglutide versus placebo during the scheduled treatment period on time to first occurrence of each of the following outcomes:

(i) SAEs by MedDRA Classification
(ii) AEs leading to permanent discontinuation of study treatment, by MedDRA Classification

2.3.1.6 Physical measurements and biochemical efficacy assessments

NHS diabetes audit data shows that weight, blood pressure, HbA1c and eGFR are monitored annually as part of routine care in at least 88% of patients with diabetes [41].

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[a] Requiring two measurements and at least 4 weeks apart unless no subsequent measurements are available by the end of the scheduled treatment period or due to death.

[b] Measurements of eGFR available up to 18 months prior to screening will be used as the baseline measurement. For those without a measurement in the last 18 months, and for whom no prior available measurement was below 60 mL/min/1.73m^2, a post randomisation eGFR below 35 mL/min/1.73m^2 will be assumed to represent ≥40% decline.

[c] Requiring continuation of dialysis for at least 4 weeks

No research samples will be taken from study participants but biochemical data (including HbA1c, blood lipids, serum creatinine, eGFR, urine albumin creatinine ratio [UACR]) from samples taken as part of routine NHS care will be obtained by linkage to routine NHS datasets. This will allow intention-to-treat analyses of the effects of allocation to oral semaglutide versus placebo on renal outcomes (see Sections 2.3.1.2 and 2.3.1.3) and on the following measures:

(i) Weight[d]
(ii) Blood pressure
(iii) HbA1c
(iv) Total cholesterol (and other blood lipids if available)

2.3.1.7 Health economic assessments

Health economic assessments will be conducted to help guide the appropriate use of oral semaglutide by health care providers. These analyses will be described in a separate health economic analysis plan. Patient Reported Outcome Measures to be collected in the trial are described in Sections 3.5.1 and 3.6.1.

2.3.1.8 Prolonged follow-up after the scheduled treatment period

Participants will be asked to provide consent to allow follow-up for 20 years after the scheduled treatment period (i.e. *long term* follow-up). This will allow longer-term assessments of the effects of approximately 5 years treatment with oral semaglutide on efficacy and safety. In particular, effects on the primary, secondary and selected tertiary and exploratory outcomes (kidney function decline, dementia/cognitive impairment, weight-related complications) and heart failure hospitalisation will be assessed at around 2, 5 and 10 and 20 years after the end of the scheduled treatment period by linkage to electronic health records.

2.3.1.9 Opportunities for adding unanticipated assessments

If, during the trial, evidence emerges from other studies to suggest that additional clinical or laboratory assessments would be of value then the protocol may be amended to include them (either in all patients or in subsets of sufficient size) during the scheduled treatment period or at the final study assessment. Given the controlled nature of the trial, comparisons between the randomised groups of outcomes assessed in this way (i.e. without a baseline assessment) can still provide a reliable unbiased assessment of the effects of oral semaglutide.

Furthermore, if any safety signals were to emerge during the monitoring of other ongoing trials of semaglutide, then more detailed and targeted collection of information related to that safety signal (e.g. validated questionnaire) could be added to subsequent study assessments. Within the context of a large blinded randomised controlled trial, such assessments would be able to provide more precise assessments of treatment effects on specific outcomes than would be provided by generic assessments.

2.3.1.10 Subsidiary analyses and sub-studies

Additional assessments and sub-populations may be defined for approved sub-studies. Details are provided in Section 6.5 and within the relevant sub-study protocol.

2.3.2 Statistical analysis

Full details of the statistical analyses will be provided in a Statistical Analysis Plan, which is to be approved by the trial Steering Committee and made publicly available prior to provision of unblinded analyses of the main trial results to any members of the Steering Committee.

[d] BMI if height data is available

At the end of the scheduled treatment period (see Section 2.7.4.4), all participants randomised to oral semaglutide will be compared with all participants randomised to placebo, irrespective of whether they received all, some or none of their allocated treatment. For the time-to-event analyses, Cox proportional-hazards model analysis will be used to test the null hypothesis of equal cause-specific hazards, with treatment allocation as a covariate, comparing all participants allocated active oral semaglutide with all those allocated placebo. Estimates of the hazard ratio will be shown with their 95% confidence intervals, and Kaplan-Meier estimates for the time to each of the primary and secondary outcomes will also be plotted (with the Cox proportional-hazards p-values). When separately assessing individual elements of composite endpoints, a participant may contribute to more than one assessment if they have events of more than one type (e.g. non-fatal ischaemic stroke followed by coronary death).

The primary assessment will be made first and will be deemed statistically significant if its two-sided p-value is <0.05. If the primary assessment shows a statistically significant benefit of oral semaglutide then the secondary assessment will also be tested at 5%. For the tertiary assessments, multiple testing will not formally be taken into account [42, 43]. Tests of heterogeneity or trend will generally be used to assess disparity in efficacy among different subgroups. Subgroup classifications will be pre-specified in the Statistical Analysis Plan.

For events listed as clinical safety assessments (Section 2.3.1.5), the number of randomised participants with at least one event will be compared using standard tests for differences in proportions. For continuous variables (Section 2.3.1.6), differences in means between the randomised groups will be assessed (based on routinely collected data), after adjustment for baseline values where possible.

2.4 SAMPLE SIZE AND PREDICTED NUMBER OF EVENTS

2.4.1 Initial assumptions

Anticipated rate of major cardiovascular events: Data from the ASCEND trial [39, 40] show that recruiting participants aged at least 55 years with no prior history of cardiovascular disease should yield a primary outcome event rate of about 1.8% per annum in placebo treated participants.

Anticipated effects of oral semaglutide on major cardiovascular events: There is good evidence from randomised trials of GLP-1 RA therapy (where adherence to treatment was variable, and the duration of some trials was relatively short) in participants with established cardiovascular disease or at very high risk thereof that these treatments are likely to lower cardiovascular risk by around 15% [26]. It is assumed that the cardiovascular risk will be proportionally reduced in this lower risk population to a similar extent.

2.4.2 Statistical power

Based on a major cardiovascular event rate in the placebo group of 1.8% per annum and median scheduled treatment period of 5 years, a trial of approximately 20,000 participants will have about 90% power at 2P<0.05 to detect a relative risk reduction in the primary outcome of 15% (Table 2).

Table 2. Statistical power to detect reductions in the primary outcome of major cardiovascular events, among 20,000 participants with median scheduled treatment period of 5 years

Outcome	Relative risk reduction	Annual event rate on placebo*	Active N=10,000	Placebo N=10,000	Power (2P<0.05)
MACE+	15%	1.8%	742 (7.4%)	868 (8.7%)	90%

* Based on event rates in the ASCEND trial (first events)

2.4.3 Planned study duration

The scheduled treatment period is planned to continue until at least 1600 participants have recorded a MACE+ (primary outcome). During the trial, the Steering Committee will review the blinded baseline characteristics of randomised participants and event rates to ensure that assumptions which may impact on statistical power remain valid. In particular, if the event rate is lower than anticipated, then the Steering Committee may consider capping the enrolment of particular groups of participants (for example, younger participants) or modifying the protocol (for example, changing the numbers of participants to be recruited) to ensure the trial has sufficient statistical power.

2.5 DATA AND SAFETY MONITORING

Previous phase III studies of various injectable GLP-1 RAs and oral semaglutide (now a marketed drug in the UK), conducted in thousands of participants, have performed systematic and detailed safety assessments (including physical examination, vital signs, electrocardiography, collection of non-serious AEs and SAEs, and haematology and biochemistry assays) and have been sufficiently large as to make unidentified clinically relevant adverse effects of semaglutide on these measures very unlikely. Consequently, the ASCEND PLUS trial focuses on the assessment of oral semaglutide on SAEs and on any AEs (serious or non-serious) resulting in the discontinuation of study treatment, based both on reports received directly from participants (or their relatives/carers or medical professionals caring for them) and on secondary use of NHS datasets and national registries. The safety reporting window will be from the day after the Run-in treatment is mailed to the participant to the end of the scheduled treatment period, unless consent is withdrawn.

2.5.1 Record linkage to routinely collected NHS datasets and national registries

Central to the conduct of the ASCEND PLUS trial will be its reliance on the efficient collection of relevant data via regular linkage to NHS datasets and registries (see Section 2.5.2.3), supplemented where necessary (see Section 2.5.2.2) by data collected from participants (or their relatives/carers) and from other healthcare professionals.

Linked NHS data received by the CCO will include:

- SAEs requiring hospitalisation;
- Attendance at Emergency Department;
- Information regarding outpatient clinic attendance;
- Information from primary care records (if available);
- Cause-specific mortality;
- Incident cancers;
- Diabetes-specific and biochemical outcomes: retinal screening results, weight, biochemistry (including HbA1c, blood lipids, serum creatinine and eGFR, UACR);
- Use of medications prescribed in primary care

The source data for these events will be the electronic files as received from these NHS datasets. For AEs, trained CCO staff blind to treatment allocation will evaluate the NHS

records to ensure the correct diagnostic code is selected in accordance with trial Standard Operating Procedures (SOP). Clinical procedures, biochemical data, weight and retinal screening results will be automatically incorporated into the trial database with limited manual intervention.

2.5.2 Recording of adverse events (AEs), including study outcomes

2.5.2.1 Definition of Adverse Events

- *Adverse Event (AE)*: any untoward medical occurrence in a participant, whether or not it is considered to be related to the study treatment

- *Adverse Reaction*: an AE which is considered to be related to the study treatment

- *Serious Adverse Events (SAEs)*: AEs that

(i) Result in death;
(ii) Are life-threatening (life-threatening refers to an AE in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe);
(iii) Require in-patient hospitalisation or prolongation of existing hospitalisation;
(iv) Result in persistent or significant disability or incapacity;
(v) Result in congenital anomaly or birth defect; or
(vi) Are important medical events in the opinion of the responsible investigator (that is, not life-threatening or resulting in hospitalisation, but may jeopardise the participant or require intervention to prevent one or other of the outcomes listed above).

(Congenital anomalies or birth defects are not expected in this trial since pregnancies are not anticipated among participants due to the age of the study population. However, were such an event to be reported to the CCO, additional information would be sought – see Section 2.5.2.4)

- *Serious Adverse Reaction*: an AE which fulfils both the criteria for a SAE and an Adverse Reaction

AEs that are not serious will only need to be collected if they are study outcomes or if they are reported as a reason for discontinuing study treatment. AEs that are not serious and do not lead to discontinuation of study treatment will not be routinely recorded as there is already sufficient evidence from previously completed trials about the effects of oral semaglutide and this class of medication on such AEs.

2.5.2.2 Reports of SAEs directly from other healthcare professionals, participants, and their relatives/carers

Participants, their relatives/carers and any doctors or healthcare professionals involved in their care will be able to contact the CCO to report a SAE at any time, and their assessment of relatedness to study treatment will be recorded. Participants will be issued with a card which they can show to any doctor (or other healthcare professional) treating them which will provide details of the trial and contact details for the CCO. If any doctor has a concern about a SAE they can contact the CCO and discuss it with a CCO study clinician (available 24-hours). During Randomisation assessments (see Section 3.5) and Follow up assessments (see Section 3.6), participants will also be asked about AEs leading to cessation of study treatment and selected study outcomes. If the CCO study team becomes aware of any SAEs, they will record them on the trial IT system.

If the SAE is reported by the participant (or their relative or carer) and the reporting individual is of the opinion that the SAE is related to the study treatment, the CCO clinician will review and, if in agreement, will follow the reporting procedures described in section 2.5.2.4. If the CCO clinician is of the view that the SAE is not related to the study treatment, then the assessment of their treating doctor will be sought. If the treating doctor considers the event to be related with reasonable possibility[e] to study treatment (and the treating doctor has confirmed that the event is serious), the CCO study clinician will follow the procedures for a suspected Serious Adverse Reaction (SAR; see Section 2.5.2.4). If the treating doctor's assessment is that the SAE is not related to study treatment, then the assessment of relatedness for the SAE will be updated. The recording of relatedness by the source will not be downgraded by CCO staff without agreement of the reporting party or their treating doctor. If the treating doctor is not available or cannot be contacted, the relatedness reported by the source will remain unchanged. The record of any such SAE which is recorded directly into the trial IT system will be considered the source data.

2.5.2.3 Linkage with routinely collected NHS datasets to identify SAEs

All participants will be 'flagged' with relevant routinely collected NHS datasets and registries including NHS England (formerly NHS Digital) and other national bodies. Such data will be received by the CCO at regular intervals during the trial follow-up period. Hospitalisations, deaths, cancers and any other relevant events identified by such linkage will be recorded as SAEs in the study database.

2.5.2.4 Collection of Additional Information for Serious Adverse Reactions (SARs)

Any SAE that is considered, with a reasonable possibility, to be due to study treatment by either a treating doctor, or the reporting party, if the opinion of the treating doctor is not available, or the CCO study clinicians is, potentially, a SAR. In making this assessment, there should be consideration, based on the available information, of the likelihood of an alternative cause, the timing of the event with respect to study treatment, the response to withdrawal of the study treatment, and the frequency of the event in the trial population. CCO study clinicians are available at all times to discuss potential cases. The CCO study clinician will seek standard information (including a description and timing of the event, and the reason for attribution to study treatment) and will then review the event for seriousness and relatedness. Any additional information required will be sought (e.g. medical history, treatment before and after randomisation and potential alternative aetiology), and expectedness will be assessed.

Only SAEs reported to the CCO directly will be considered as potential SARs. Relatedness will not be recorded for SAEs identified through the linked routinely collected healthcare and registry data (i.e. secondary use of data), and therefore such SAEs will not be considered as potential SARs.

2.5.2.5 Exemptions and expedited reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

SARs will be reviewed by CCO study clinicians to assess the need for expedited reporting. As is recommended by the FDA [44], anticipated events that are either efficacy endpoints, consequences of the underlying disease, or common in the study population will be exempted from expedited reporting in order to protect trial integrity and because, based on a single case, it is not possible to conclude that there is a reasonable possibility that the investigational drug caused the event [45, 46]. Thus the following events will be exempted from expedited reporting (as SUSARs):

[e] https://database.ich.org/sites/default/files/E2A_Guideline.pdf

(i) Selected efficacy endpoints: cardiovascular death, myocardial infarction, stroke, TIA, coronary or non-coronary revascularisation; hospitalisation for heart failure; NASH; kidney disease decline; dementia; and
(ii) Events which are the consequence of cardiovascular disease: angina and coronary artery disease

The relevant MedDRA Preferred Terms which are exempt from expedited reporting will be specified in the SOP for AE reporting. Any SARs that are not exempt will be reviewed by the CCO to make an assessment of whether the event is "expected" or not [44, 47]. Expectedness of SARs will be determined according to the relevant RSI section of the Summary of Product Characteristics. The RSI used (within the SmPC) will be the most recent EU version that has been approved for the purpose of the trial at the time of the event occurrence.

Any SAR that is considered to be "unexpected" will be considered a potential Suspected Unexpected Serious Adverse Reaction (SUSAR) and will be unblinded at the CCO (with knowledge of the treatment allocation limited to the Principal Investigators). All confirmed SUSARs will be reported to relevant regulatory authorities, ethics committees and investigators in an expedited manner in accordance with regulatory requirements as defined in the study "Capture, communication and regulatory reporting of Adverse Event information" SOP.

2.5.3 Development Safety Update Report

The University of Oxford will be responsible for preparing and submitting a study specific Development Safety Update Report (DSUR) in collaboration with Novo Nordisk. The DSUR will include all SAEs reported during the study (including both those reported directly by healthcare professionals, participants, and their relatives/carers, and those identified through linkage with routinely collected healthcare data – see Sections 2.5.2.2 and 2.5.2.3).

2.5.4 Safety review during the trial

2.5.4.1 Role of the DMC

A Data Monitoring Committee (DMC) Charter, describing in detail the roles and responsibilities of the independent DMC, including the methods of providing information to and from the DMC, frequency and format of meetings and statistical considerations will be approved by the trial Steering Committee and agreed by the DMC at the first DMC meeting.

2.5.4.2 Frequency of reviews

During the study, analyses of all SAEs and other study outcomes will be supplied in strict confidence to the independent DMC. The DMC will request such analyses at a frequency relevant to the stage of the study (typically at 12 monthly intervals, with a Chairman's review approximately every 6 months) or in response to emerging data from other studies.

2.5.4.3 Early stopping for hazard

The DMC is expected to advise the Steering Committee if clear and consistent evidence emerges (either overall or in a particular subgroup of patients) of a compelling adverse effect, for example an adverse effect on all-cause mortality of at least 2 standard deviations in the test statistic (unless there are some mitigating circumstances, such as small numbers of deaths or inconsistent results for fatal and non-fatal events) or if, in the view of the DMC, there is other compelling evidence of hazard that seems likely to outweigh any potential benefit (e.g. a later reduction in cardiovascular events). For the avoidance of doubt, the DMC

will therefore review un-blinded analyses of the primary and secondary efficacy outcomes in order to inform any decision on stopping for hazard.

2.5.4.4 Early stopping for benefit

No interim analysis for benefit is planned.

2.5.4.5 Role of the Steering Committee

If the Steering Committee receives advice from the DMC to recommend early stopping, it will decide whether to modify the study, or to seek additional data. Unless this happens, the Steering Committee, collaborators, study participants, representatives of Novo Nordisk, and all study staff (except those who provide the confidential analyses to the DMC) will remain blind to the interim results on mortality and morbidity until the end of the study.

2.6 BIOLOGICAL SAMPLES

No research-specific blood or urine samples will be collected from participants. Measurements of HbA1c, lipids, urine albumin, UACR and creatinine undertaken by the participants' usual doctors as part of routine care will be sought and obtained from NHS healthcare data linkage.

2.7 CENTRAL COORDINATION OF THE TRIAL

The study will be coordinated by the CCO based at the University of Oxford. Responsibilities for the CCO are described in Section 6.1.

2.7.1 Clinical support

Participants and other healthcare professionals will have access to the study Freephone number at any time. CCO study clinicians, or other research staff, will be available to respond to queries from participants or their doctors. CTSU runs an after-hours on-call rota for our ongoing trials, staffed by trained CCO study clinicians. The participant's GP will be informed of any relevant advice given to participants, such as recommended changes to their usual diabetes medication.

Throughout the trial, clinical management, including non-study glucose-lowering therapies, healthy lifestyle guidance and continuation of NHS retinal screening, will remain the responsibility of the participant's usual doctors, although interim advice may be provided by the study team when advice is sought by participants or their family/carers.

2.7.2 Local study sites

The National Institute for Health and Care Research (NIHR) will identify collaborating NIHR or NHS institutions able to provide research coordinators (research nurses, or other staff with suitable training and experience to support the trial). They will be available to contact any participants who request to complete their screening, randomisation or follow-up assessments by telephone or video call, have questions about the study during the online informed consent process or would like to speak to a research coordinator about side effects or any other aspect of the trial. These local research coordinators will be research nurses, allied health professionals or other individuals, such as clinical research practitioners, with suitable training and experience to undertake study assessments (including the seeking informed consent) and respond to questions from participants. They will be supported by CCO clinicians who can provide advice (for example to advise participants who are receiving treatment with insulin or a sulphonylurea about adjustment of their therapy if needed). The activities undertaken by staff at these sites as part of the trial will be overseen by a local

investigator who may be a clinician or a senior nurse or other qualified healthcare professional. The sites will not be involved in management of the study treatment and will not be responsible for routinely collecting SAE information. However, if site staff become aware that an SAE has occurred then they will notify the CCO. Due to the design of the trial, where a participant might communicate with different research coordinators based in different parts of the UK over time, local research coordinators will not have individual participants linked to only their site and they will therefore not be responsible for ensuring protocol adherence for particular participants. They will however be responsible for undertaking particular trial activities.

2.7.3 Quality assurance

The study will be conducted in accordance with the principles of Good Clinical Practice (an internationally recognised standard for the conduct of clinical trials) and relevant local, national and international regulations. The study uses FDA-recommended Quality-by-Design approaches to help ensure the quality of the study design and operations prospectively (rather than aiming to identify issues retrospectively) [48]. The focus will be on those factors that are critical to quality (i.e. the safety of the participants and the reliability of the trial results).

2.7.3.1 Training

The Principal Investigators at the University of Oxford will be responsible for ensuring CCO staff are trained in relevant study procedures according to their role. The CCO will also train research staff at study sites in the study procedures (including use of the trial IT systems).

2.7.3.2 Monitoring

Throughout the study, the CCO will monitor critical factors (such as rates of recruitment, adherence to study medication, completeness of follow-up assessments by participants), so that the focus remains on issues with the potential to have a substantial impact on the safety of the study participants or the reliability of the results.

No site monitoring visits will be required since there are no in-person visits in the trial. However, the CCO will monitor activities of research coordinators at local sites. The purpose of such monitoring activities will be to ensure that the study is being conducted in accordance with the protocol, particularly through helping research staff to resolve any problems and providing extra training focussed on specific needs. In addition, the CCO will monitor activities of the UK-based contract distributer which stores and mails study treatment to participants, and will have the right to conduct on-site audits.

2.7.3.3 Serious breach reporting

A serious breach is defined as “a breach of GCP or the trial protocol which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial”.

In the event that a serious breach is suspected, the CCO must be informed within 1 working day. In collaboration with the Principal Investigators at the CCO, the serious breach will be reviewed by the University of Oxford Research Governance, Ethics & Assurance Team and, if appropriate, it will be reported to the REC, Regulatory authority and relevant NHS sites within seven calendar days.

2.7.3.4 Access to data for audit

Direct access will be granted to authorised representatives from the University of Oxford Research Governance, Ethics & Assurance Team, the regulatory authorities and Novo Nordisk to permit audits and inspections. Consent will be sought from participants for this.

2.7.4 Administrative details

2.7.4.1 Source documents and archiving

Source documents for the study constitute the screening, randomisation and follow-up assessment records held in the study main database, information obtained by linkage from NHS datasets, records of SAEs that are reported directly to the CCO, and drug supply records. These will be retained for at least 25 years from the end of the long term follow up period (see Section 2.3.1.8). The study database will remain under the control of the Principal Investigators at CTSU. A full audit trail of any changes made to the data will be available. Novo Nordisk and regulatory agencies will have the right to commission confidential audits of such records in the CCO provided that this does not result in un-blinding while the study is in progress.

2.7.4.2 Sponsor and funding

This study was initiated and designed by independent scientists at CTSU, University of Oxford. The University of Oxford will act as sponsor of the trial. Responsibilities for different aspects of the trial for the CCO and Novo Nordisk will be set out formally in legal agreements and SOPs. A safety data exchange agreement between the sponsor (Oxford University) and the funder (Novo Nordisk) will be prepared describing potential safety reporting obligations of the funder. Novo Nordisk will provide funding and study medication (oral semaglutide and matching placebo) for the study.

Delegation from the Chief Investigator (based at the CCO) to Principal Investigators (also based at the CCO who will assume some investigator responsibilities such as management of IMP, AE reporting and responsibility for protocol adherence) and from them to the other study staff will be recorded.

2.7.4.3 Indemnity

The University has a specialist insurance policy in place which would operate in the event of a participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS staff will be indemnified through contracts between their employer and the University of Oxford. Novo Nordisk indemnifies the University of Oxford against any third party claims that result from the Investigational Medicinal Product (IMP) and its failure to comply with Good Manufacturing Practice (GMP) and/or applicable law.

2.7.4.4 End of trial

At the end of the scheduled treatment period, participants will receive a final participant questionnaire along with instructions to stop the study treatment. However, data collection will continue until the final data linkage covering the scheduled treatment period is received by the CCO. It is planned that long-term follow-up of all surviving randomised participants will then continue for the subsequent 20 years in order to provide valuable information on the longer-term safety and efficacy of oral semaglutide.

2.7.4.5 Publications and reports

The Steering Committee will be responsible for drafting the main reports from the study and for review of any other reports. The Steering Committee will establish a publication plan for primary publications, secondary publications and exploratory analyses. In general, papers initiated by the Steering Committee (including the primary manuscript) will be written in the name of the Collaborative Group, with individual investigators named personally at the end

of the report (or, to comply with journal requirements, in web-based material posted with the report).

The Steering Committee will also establish a process by which proposals for additional publications (including from independent external researchers) are reviewed and approved. The process will be agreed upon and approved by the Steering Committee. The Steering Committee will facilitate the use of the study data and approval will not be unreasonably withheld. However, the Steering Committee will need to be satisfied that any proposed publication is of high quality, honours the commitments made to the study participants in the consent documentation and ethics committee approvals, and is compliant with relevant legal and regulatory requirements (e.g. relating to data protection and privacy). The Steering Committee will have the right to review and comment on any draft manuscripts prior to publication.

2.7.4.6 Sub-studies

Proposals for sub-studies must be approved by the Steering Committee, the Sponsor and by the relevant ethics committee and competent authorities (where required) as a substantial amendment or separate study before they begin. In considering such proposals, the Steering Committee will need to be satisfied that the proposed sub-study is worthwhile and will not compromise the main study in any way (e.g. by reducing the recruitment rate or adherence with study treatment and follow-up). Details of approved sub-studies are provided in Section 6.5.

3 SUMMARY OF PRACTICAL PROCEDURES

PRE-SCREENING PHASE
• Potentially eligible individuals identified from routinely collected healthcare datasets • Invitation to join the study by letter and initial information (telephone support available) • Full participant information leaflet sent to those who express interest
SCREENING ASSESSMENT (APPROXIMATELY -16 to -8 WEEKS)
• Participants choose initial screening method (online questionnaire or by telephone or video call) • Initial agreement for recording of screening information • Self-reported medical history and other eligibility factors recorded • Informed consent sought from participant and recorded • Discussion (by telephone or video call) to record consent and/or answer questions if requested by participant, and/or to clarify any questions regarding eligibility (if initially using online questionnaire) • Data for potentially eligible participants reviewed by CCO study clinician
PRE-RANDOMISATION RUN-IN PHASE (APPROXIMATELY -12 TO -8 WEEKS)
• Letter mailed to GP regarding provisional entry into the trial • Run-in consisting of 4-week active 3mg oral semaglutide and 4 to 8-week active 7mg oral semaglutide; taken as one tablet daily starting with 3mg bottle, then 7mg bottles. Study treatment is mailed to participant with instructions. • All participants can contact the CCO or request to be contacted by study staff
RANDOMISATION ASSESSMENT (0 WEEKS)
• Participant requested to complete the randomisation questionnaire online or by telephone or video call with a research coordinator • Eligibility and consent checked • Self-reported height and weight recorded • Quality-of-Life assessment (to inform health economic analyses) • Minimised randomisation undertaken by the CCO • Allocated oral semaglutide (starting dose 14mg daily) or placebo • Letter mailed to GP to inform them of their patient's randomisation • First 24-week pack of randomised study treatment (semaglutide 14mg or placebo) mailed to the participant with instructions; taken as one tablet daily • All participants can contact the CCO or request to be contacted by study staff
FOLLOW-UP ASSESSMENTS AND PROVISION OF STUDY TREATMENT (APPROXIMATELY 12 WEEKS, 24 WEEKS AND THEN ~24 WEEKLY)
• Participant requested to complete follow-up questionnaire online or by telephone or video call at approximately 12 weeks, 24 weeks and every 24 weeks • Any reasons for stopping study treatment and selected study outcomes recorded • 24-week pack of randomised study treatment mailed to the participant approximately every 24 weeks; taken as one tablet daily • Additional patient reported outcomes collected at some assessments • All participants can contact the CCO or request to be contacted by study staff
FINAL STUDY ASSESSMENT
• Participant requested to complete final follow-up questionnaire online or by telephone or video call • Quality-of-Life assessment (to inform health economic analyses)
MONITORING OF SAFETY AND EFFICACY
• Data for safety and efficacy outcomes obtained by participant or healthcare professional report or linkage to NHS datasets and national registries • Further information about relevant outcomes sought from participant's doctor where necessary • Relevant events assessed centrally by CCO study clinicians, blind to treatment allocation

3.1 ELIGIBILITY FOR THE STUDY

Patients are eligible for the study if:

- The inclusion criteria are satisfied; and
- None of the exclusion criteria applies; and
- They are willing and able to provide informed consent

3.1.1 Inclusion criteria

All of the following must be satisfied:

(i) Adults aged at least 55 years at the time of the Screening assessment
(ii) T2DM (based on self-reported medical history)

3.1.2 Exclusion criteria

None of the following must apply (based on self-reported medical history):

(i) Myocardial Infarction
(ii) Stroke
(iii) Current or planned treatment with a GLP-1 RA
(iv) Previous hypersensitivity to or intolerance of GLP-1 RA therapy[f]
(v) Severe hypoglycaemia[g] within the last six months or during run-in
(vi) Symptomatic hypoglycaemia[h] within the last month[f]
(vii) Currently under consideration to commence insulin[f]
(viii) Severe heart failure (NYHA class 4)[f]
(ix) Current or planned renal replacement therapy[f]
(x) Unwilling to complete regular follow-up assessments
(xi) Ongoing treatment for cancer or diagnosis with cancer (excluding non-melanoma skin cancer) in the last 2 years
(xii) Type 1 or other type of diabetes (e.g. MODY)[f]
(xiii) History of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma[f]
(xiv) Currently breastfeeding or pregnant, or planning a pregnancy[f]
(xv) Any serious illness which is likely to limit survival or active participation for at least 5 years
(xvi) Current participation in a clinical trial with an unlicensed investigational medicinal product used to treat diabetes[f]
(xvii) For participants taking thyroxine, lack of agreement to arrange a thyroid function test in the next 3 months and agree to regular testing throughout the trial[f]
(xviii) Non-adherence to run-in treatment (i.e. reports taking the run-in tablets 'Never' or 'Only occasionally' (see Section 3.5.1)
(xix) Their doctor does not wish them to be randomised (see Section 3.4).

Further details of the assessment of eligibility are provided in Section 3.3.1.

3.2 IDENTIFICATION AND INVITATION TO PARTICIPATE

Lists of potentially eligible individuals will be generated from electronic searches of centrally held NHS datasets by information specialists at NHS England or equivalent NHS bodies in England, Wales and Scotland. The searches will identify people of appropriate age with

[f] Assessed at screening only
[g] Low blood glucose requiring attendance at Accident and Emergency or urgent bystander intervention
[h] Symptoms such as shaking, sweating, confusion and hunger, with either a blood glucose level less than 4 mmol/L or improvement with sugar intake if blood glucose monitoring not available

T2DM (who do not have a recorded history of myocardial infarction, stroke or recent cancer or selected other exclusion criteria depending on the available data). With appropriate privacy approvals, these data will be used to generate invitation letters which will be mailed to potential participants and which will include an initial information leaflet. The University of Oxford will not have access to personally identifiable information for any patient invited in this way unless they declare interest in the trial (e.g. by returning a reply form to the CCO). Participants who express interest in the trial will be mailed the full participant information leaflet and data protection information. In addition, the CCO holds identifiable data for participants from the ASCEND trial who have agreed to future contact for other studies. Invited patients who are interested in joining the trial will be able to access the trial IT system (or contact the CCO by telephone) to complete a Screening assessment. As part of a sub-study, some potentially eligible patients identified by NHS England will be randomised to receive one of (i) a control invitation letter (ii) an invitation letter with an altruism behavioural nudge (iii) an invitation letter with an individualism and norms behavioural nudge (see Section 6.5).

3.3 SCREENING ASSESSMENT

3.3.1 Assessment of relevant medical history and eligibility

Participants will be offered a choice of completing the Screening questionnaire and informed consent either via a telephone or video call with a research coordinator or by attempting the self-directed Screening and consent process online. In either case, potential participants will be asked to record initial consent for data about their medical history and eligibility to be recorded. The participant will be required to enter, or provide, a personal identifier (e.g. partial date of birth) to confirm their identity. Participants who have provided consent for the eligibility assessment will then complete a Screening questionnaire (via the trial IT system or telephone/video call) which is designed to establish their eligibility for the trial and record key information including whether they take any insulin, GLP-1 RA or oral hypoglycaemic therapy to treat their diabetes. This is on the background of the initial identification of the participant based on a search of key criteria (including age, the absence of any record of myocardial infarction or stroke or recent cancer, and other criteria as available) held in NHS datasets (see Section 3.2).

Those individuals who choose to complete the self-directed Screening and informed consent will be able to contact the CCO with any questions or to request a telephone or video call from a research coordinator (supported by CCO study clinicians where necessary) to answer any questions. Recording of particular responses on the screening questionnaire will automatically require a telephone or video call with a research coordinator and, in addition, CCO clinicians will contact participants to resolve any uncertainties which arise based on their completion of the screening assessment questions with contact with a participant's GP if necessary. Individuals will be discouraged from participating if it is thought unlikely that they would be adherent to the study treatment and/or continue completing Follow-up assessments for at least 5 years.

3.3.2 Consent to participate

After completing questions about eligibility, participants completing the Screening assessment online will be required to review consent materials based within the study IT applications, accessible via a computer, smartphone or tablet (including a video providing relevant information about the trial in an easy to understand format) and will be asked to provide their written (electronic) informed consent to enter the trial. Each individual will have the opportunity to discuss any aspect of the trial by contacting the CCO by Freephone or email, or by requesting a call (telephone or videoconference) back from a research

coordinator. Where requested or necessary, the informed consent discussion will be conducted over the phone or by video call with trained research staff. Wherever possible, consent will then be documented by the participant themselves using an online consent form. If this is not possible (e.g. the participant has no access to the internet), the research coordinator will document the consent during the call with the participant, and paper copies will then be mailed to the participant which the participant will be asked to sign and return to the CCO. Consent to collect routinely collected healthcare data from NHS providers and other national bodies for the scheduled 5-year scheduled treatment period and the subsequent 20 years will be requested as part of the main trial consent. A sample of individuals who have completed some or all of the trial's consent process will be invited to take part in an optional qualitative evaluation of participants' experiences of the ASCEND PLUS consent process (see Section 6.6.1).

3.4 RUN-IN PERIOD PRIOR TO RANDOMISATION

Screening assessment data for participants who consent to join the study will be reviewed by a Principal Investigator at the CCO (or appropriately delegated and trained CCO study clinician) who will be required to electronically sign, with their unique username and password, that they are satisfied that the participant is eligible for the trial, having resolved any uncertainties arising from the screening questions, and confirm that study treatment may be given according to the protocol. This approval will remain valid for the entire trial unless the dose is reduced or study treatment is stopped. If a change in dose or restart following discontinuation of randomised study treatment is needed at a later point, this will be electronically authorised by a Principal Investigator or their deputy. Participants who are not considered eligible will be withdrawn at this point, while those who are considered eligible will enter the run-in period.

The intention of this phase is to identify participants who are less likely to remain adherent with study treatment during the randomised phase, thereby maximising exposure to regular dosing with oral semaglutide daily, and also to allow a participant's GP to consider their participation prior to randomisation. Electronic confirmation of eligibility in the trial IT system will trigger the sending of a letter to the participant's GP, providing information about the trial and confirming that the patient under their care wishes to join the trial. The GP will be given the opportunity to indicate whether, in their view, there are any factors that make the patient unsuitable to join the study (under which circumstance the participant will be withdrawn from run-in).

Entry into run-in will also trigger the mailing of an initial active run-in pack of study treatment along with instructions. The run-in phase consists of 4-week active 3mg oral semaglutide (1 bottle) and 4 to 8-week active 7mg oral semaglutide (2 bottles supplied), to be taken as one tablet daily starting with 3mg bottle, followed by the 7mg bottles. Participants will be given information about the medication and advised how to transition from the 3mg to the 7mg tablets. Instructions will be provided to take one tablet fasting in the morning, at least 30 minutes before eating or drinking and with up to half a glass of water. An ascending dose active run-in is preferred to a placebo run-in given that gastrointestinal side-effects (such as nausea) are common, but often transient, on GLP-1 RA therapy and typically occur during treatment initiation and dose escalation. Participants will be able to cease the run-in treatment at any point and withdraw from run-in. Participants will be advised that they may experience hypoglycaemia if they are also taking insulin or treatment with a sulphonylurea, and will be advised to be vigilant for symptoms of hypoglycaemia. They will also be able to

contact the CCO or to request a telephone or videoconference call from a trial research coordinator to address any questions.

During the run-in period, any SAEs reported to the CCO will be recorded in the trial IT system.

3.5 Randomisation Assessment (0 months)

3.5.1 Final check of eligibility before randomisation

Individuals who have not withdrawn from run-in will be requested to complete a questionnaire (within the trial IT system or by telephone/video call) regarding whether they have experienced a myocardial infarction or stroke during the run-in period, or any other significant problems which will prevent them from entering the randomised phase of the trial. Self-reported adherence to the run-in medication will be collected (i.e. a response to the question 'How regularly have you been taking your ASCEND PLUS medication since you received it?'; 'Every day'; 'Most days'; 'Only occasionally'; 'Never'). If they report taking the run-in medication 'Only occasionally' or 'Never' or have experienced a myocardial infarction, stroke or other significant medical problem likely to limit survival or active participation in the trial (see Section 3.1.2) during the run-in, then they would not be eligible for randomisation and would not continue in the trial. Failure to complete the randomisation assessment by 14-weeks after entering the run-in period will also result in withdrawal from run-in. Otherwise, completion of the randomisation assessment will allow the participant to be randomised into the trial. Information about smoking history and alcohol intake will be sought and an assessment of quality of life will be made (using the EQ-5D instrument) at this point.

3.5.2 Random allocation of study treatment

Eligible and consenting individuals who confirm that they wish to fully enter the trial will be allocated oral semaglutide or placebo using a minimised randomisation program in the trial IT system that helps to maximise balance between the treatment groups with respect to prognostically important variables including age, sex, smoking status, current insulin treatment, history of any revascularization procedures, duration of diabetes. The algorithm includes a stochastic element, with treatment assigned to the group identified by the algorithm to minimise differences between the groups with a probability of 0.95.

After randomisation, a letter will be sent to their GP confirming that their patient has formally entered the main trial. The first pack of blinded study treatment (either oral semaglutide 14mg per day or placebo for all participants) will then be mailed to the participant along with instructions regarding recommendations for taking the tablets.

3.6 Follow-up Assessments (scheduled at 12 and 24 weeks, then every 24 weeks)

3.6.1 Information collected during follow-up assessments

Information is to be collected from all study participants, irrespective of whether or not they continue to take the study treatment. Following randomisation, all participants will be prompted to complete a Follow-up assessment (via online questionnaire or by telephone or video call) at around 12 weeks, 24 weeks and then about once every 24 weeks until the end of the scheduled treatment period. Information about insulin or GLP-1 RA use, any reason for discontinuing study treatment (including relevant AEs or non-medical reasons) and the occurrence of any myocardial infarction, stroke or TIA will be recorded online by participants, or by interview with study staff who enter participants' responses directly into the trial IT system. Participants will not be asked to provide details of other AEs which have not led to

discontinuation of study treatment. Participants will be able to contact the CCO at any time or to request a telephone or videoconference call from a trial research coordinator.

Information on relevant outcomes, including all hospitalisations, deaths and incident cancers, will be sought via regular linkage to NHS and other national datasets as described in Section 2.5.1. Study staff may be notified of SAEs at any time (either directly by participants or by their relatives, carers, or other clinical staff), so this information can be captured on the trial IT system at any time.

Participants will be asked to complete the Veterans RAND 12 Item Health Survey (VR-12) early during the scheduled treatment period (1-2 years after randomisation), and both the VR-12 and the Problem Areas In Diabetes (PAID) scale later in the scheduled treatment period (3-4 years after randomisation). As part of the final Follow-up assessment at the end of the scheduled treatment period, a further assessment of quality of life will be made (using the EQ-5D instrument).

3.7 PROVISION OF STUDY TREATMENT AFTER RANDOMISATION

Provided that continuation of study treatment remains appropriate, participants will be mailed packs of their randomly allocated study treatment (oral semaglutide or placebo) approximately once every 24 weeks. Participants taking daily oral semaglutide 14mg (or matching placebo) will be able to reduce the dose to 7mg daily (or matching placebo), for example to limit any gastrointestinal symptoms. It may be necessary to delay mailing out a pack of study treatment if safety concerns arise or a participant is otherwise unable to receive it (e.g. due to travel). Following such a delay, study treatment will be resupplied as soon as possible which may result in subsequent supplies of study treatment shifting from the original schedule. If a participant reports discontinuing study treatment and is subsequently willing to recommence study treatment, this will be facilitated, unless the Principal Investigators at the CCO, or their deputy, have deemed it inappropriate to do so (for example following a SAR). When a participant restarts study treatment after a prolonged period off treatment they will be asked to restart study treatment with 4-weeks of 3mg/placebo tablets (1 bottle) and then 4 to 8-week 7mg/placebo tablets (2 bottles supplied) in order to limit the risk of suffering gastrointestinal symptoms. This will usually be required if participants have been off study treatment for one month or longer. They will then revert to 14mg semaglutide or matching placebo daily (or remain on 7mg semaglutide or matching placebo if that is their preference).

3.8 MODIFYING OR UNBLINDING STUDY TREATMENT

3.8.1 Modifying study treatment

The following events are considered sufficient reason to discontinue the study treatment:

(i) SAE considered with reasonable possibility to be due to the study treatment (see Section 2.5.2.4);
(ii) Commencement of GLP-1 RA treatment as part of usual care;
(iii) At the request of the participant or their usual doctor/s;
(iv) Any other situation where continuing study treatment is not considered to be in the participant's best interests by their usual doctor/s or the CCO study clinicians.

At present there are no clinical conditions or medications which are contraindications to continuation of study treatment. Participants who meet one of the exclusion criteria listed in

Section 3.1.2 *after* randomisation may continue with the study treatment, unless there is a particular reason not to do so.

When study treatment stops at the end of the scheduled treatment period, it will no longer be made available to participants unless it is prescribed by their usual doctor.

3.8.2 Unblinding of study treatment

Urgent unblinding of the treatment allocation (oral semaglutide or placebo) is available on a 24-hour basis via the CCO Freephone telephone service. Requests for unblinding will be considered, and authorised, rapidly by an on-call CCO clinician. There are two main situations in which unblinding for an individual participant would be warranted:

(i) When knowledge of the treatment allocation could materially influence the immediate medical management of the patient; and
(ii) When a Principal Investigator (or their deputy) processes the report of a confirmed SAR to determine whether the patient is receiving active semaglutide (see Section 2.5.2.5) except for SARs which are expected and SUSARs which are exempted from expedited recording.

For the avoidance of doubt, if a treating doctor requires the unblinded treatment allocation, this information will not be withheld.

3.8.3 Withdrawal of consent by randomised participants

A decision by a randomised participant that they no longer wish to continue to receive study treatment or complete follow-up assessments should not be considered to be complete withdrawal of consent for all follow-up.

Participants are free to withdraw consent for some or all aspects of the study at any time if they wish to do so. In order to ensure that relevant safeguards are in place to maintain participants' safety (e.g. if an important safety issue comes to light that might affect a participant who has previously withdrawn their consent) and to prevent a breach of the individual's decision (e.g. to avoid re-invitation after withdrawing consent), withdrawal of consent for any aspect of follow-up will be recorded. Recorded details will include whether the request was made by the participant directly or a relative, carer, friend or other source; confirming the degree of consent withdrawal (such as whether consent has also been withdrawn for collection of follow-up information from the participant's health records). In accordance with FDA guidance, data that have already been collected up to the point of consent withdrawal will continue to be used.

3.9 CONFIRMATION OF STUDY OUTCOMES

Previous cardiovascular outcome trials run by CTSU have adjudicated cardiovascular outcomes based on initial participant report, and have also collected information regarding cardiovascular events from routinely collected NHS datasets. Comparisons of adjudicated outcomes and outcomes derived from hospitalisation data show good agreement for events which usually require hospitalisation such as cardiovascular death, myocardial infarction, hospitalised stroke, and coronary and non-coronary arterial revascularisation, but poor sensitivity for events which typically do not require hospitalisation such as TIA [49]. Information regarding hospitalisations received via data linkage will be reviewed by the CCO study clinicians to ensure that the diagnosis recorded appears correct in the context of the overall clinical record. Following a pre-specified SOP the CCO clinicians, blind to treatment allocation, may select a more appropriate diagnostic code if necessary. No additional

information will usually be routinely sought regarding these SAEs. SAEs reported directly to the CCO will be recorded into the trial IT system and coded into MedDRA; potential study outcomes identified from ad hoc direct reporting to the CCO or reported by the participant during their follow-up assessment, but not found in linkage datasets, will require additional confirmation. Such confirmation may be obtained from other information in the linkage data (e.g. attendance at a relevant outpatient clinic and initiation of particular therapy) or from discussion with the participant or their GP.

4 INVESTIGATIONAL MEDICINAL PRODUCT

4.1 NAME AND DESCRIPTION OF THE INVESTIGATIONAL MEDICINAL PRODUCTS

The active study treatment to be used in ASCEND PLUS is oral semaglutide in the form of 3mg, 7mg and 14mg tablets. The control will be placebo tablets to match the 3 mg, 7mg and 14mg semaglutide tablets (see Table 3). Study treatments will be provided by Novo Nordisk A/S, Denmark. Oral semaglutide is licensed for the treatment of adults with insufficiently controlled T2DM to improve glycaemic control as an adjunct to diet and exercise in the UK, European Union (EU) member states, and the US. The marketing authorisation holder is Novo Nordisk.

Table 3. Trial product provided by Novo Nordisk A/S

Trial product	Strength	Dosage form	Route of administration	Container/ delivery device
Semaglutide 3 mg tablet (IMP, test product)	3 mg	Tablet	Oral	HPDE container of 28 tablets
Semaglutide 7 mg tablet (IMP, test product)	7 mg			
Semaglutide 14 mg tablet (IMP, test product)	14 mg			
Placebo tablet (IMP, reference therapy)	NA			

4.2 IMP PREPARATION, STORAGE, LABELLING AND SUPPLY

Novo Nordisk will be responsible for packaging, labelling and Qualified Person (QP) release of uniquely identifiable packs of finished study IMP in accordance with GMP standards.

Packs will be delivered according to an agreed schedule to the trial's UK-based contract distributer. Under the instruction of the CCO, the contract distributer will be responsible for:

- storage of released packaged IMP
- selection and preparation for dispatch of specified bottles of packaged IMP assigned to specified study participants
- providing UK based QP oversight in line with MHRA requirements

IMP labels will be designed in accordance with Annex 13 of the EU GMP Guide. The CCO will maintain an inventory and audit trail of all bottles of study IMP on the trial IT system. In addition, the trial IT system will record any bottles of study IMP that have expired or been damaged prior to being assigned to study participants, as well as a record of their subsequent destruction. All bottled study IMP will be labelled with an expiry date beyond which it should not be used, and will only be issued to participants with due allowance for the remaining shelf life.

At the randomisation assessment and each follow up assessment, information on the participant's willingness to continue to receive study treatment by post will be recorded into the trial IT system. In addition, CCO study clinicians will be able to discontinue the provision of study treatment to any participants considered unsuitable to receive further study treatment (e.g. in the case of a SAR). The trial IT system will thus determine whether, according to the protocol, it is appropriate to assign and mail a further pack of study treatment at the relevant time and, if it is, a pack will be identified by the trial IT system to be mailed to the relevant participant.

4.3 MAIL-OUT OF STUDY TREATMENT

All packs of study IMP assigned to study participants will be sent by Royal Mail standard post, on instruction from the CCO (though other courier providers may be used for urgent deliveries on occasion). Royal Mail will be responsible for delivering packs of study treatment assigned to specified study participants. At the point of dispatch of packs of study treatment by the UK-based contract distributer via Royal Mail, a participant identifier ancillary label will be applied to each pack. Steps will be taken to further ensure the reliability of this method of delivery including automated message (i.e. SMS texts, emails) to inform participants that their study medication is en route and requesting that they contact the CCO if it is not received in the coming days.

The mail-out of study treatment has been an effective approach for other trials conducted in the UK such as the 15,000 participant ASCEND trial [39, 40], the FAST trial (https://www.fast-study.co.uk/), and the ongoing LENS trial (https://www.ctsu.ox.ac.uk/lens). In the LENS trial, 5,500 run-in and randomised treatment packs had been mailed out as of July 2020, and only 35 (0.6%) had been returned as 'undelivered' to the CCO (many of which were subsequently resupplied due to the participant being temporarily away from home).

Participants will be advised to take any expired or unused study IMP to a local pharmacy for safe disposal (as has been done for both the LENS and ASCEND trials) and to dispose of empty bottles. Due to the streamlined design of the ASCEND PLUS trial where participants will not attend sites, it is considered overly complex and prone to unacceptable risk to expect study participants to securely return study IMP via the postal system or other courier service.

The CCO will be responsible for handling and destruction of any returned, expired or unused IMP and packaging materials which it receives back from study participants or that is returned as undelivered.

4.4 DEVIATIONS FROM THE SUMMARY OF PRODUCT CHARACTERISTICS

In the ASCEND PLUS trial, the administration of active study treatment will deviate from the EU Summary of Product Characteristics (SmPC), updated 11 April 2024, as follows:

4.4.1 Therapeutic indications

The SmPC states that oral semaglutide may be considered as monotherapy when metformin is considered inappropriate due to intolerance or contraindications. ASCEND PLUS will include participants on no glucose-lowering therapy given that current evidence suggests that cardiovascular and renal benefits are unlikely to be driven by lower glucose levels, suggesting that those on no diabetes medicines are similarly likely to derive benefit as those on such medicines if the trial is positive. Of note, major cardiovascular outcome trials of semaglutide are now underway in participants without diabetes.

4.4.2 Posology

Usual practice is to commence oral semaglutide at a dose of 3mg daily for one month, followed by 7mg for one month, at which point the patient is titrated up to 14mg daily (if tolerated). In ASCEND PLUS it is important that (i) participants are randomised and are able to commence their randomised study treatment (placebo or semaglutide 14mg daily) before they run out of 7mg active run-in tablets, and (ii) that they are exposed to the 7mg run-in dose for sufficiently long to test their tolerance of the study treatment. Therefore, the trial run-in pack includes 4-weeks (1 bottle) of 3mg tablets and 8-weeks (2 bottles) of 7mg tablets,

and the intention is to randomise participants while they are using the second 7mg tablet bottle wherever possible and with sufficient 7mg tablets remaining to last until the first randomised pack of study treatment arrives by post.

4.4.3 Effects of semaglutide on other medicinal products

The SmPC states that upon initiation of oral semaglutide treatment in patients on warfarin, frequent monitoring of INR is recommended (though there is no data to show any change in AUC or Cmax of R- and S-warfarin) that cases of decreased INR have been reported during concomitant use of acenocoumarol and semaglutide The trial investigators will not be able to mandate the frequency of monitoring of INR but will provide this information as written advice to the participants and their GP. Oral semaglutide may increase total exposure to thyroxine. The trial investigators will not be able to mandate the frequency of thyroid function tests but will advise participants to undergo testing within 3 months of screening, and will advised both participants and their GP of the importance of regular monitoring.

5 REFERENCES

1. *International Diabetes Federation. IDF Diabetes Atlas*. 2019; Available from: https://www.diabetesatlas.org/en/. (last accessed 07 July 2022)
2. Rao Kondapally Seshasai, S., et al., *Diabetes mellitus, fasting glucose, and risk of cause-specific death.* N Engl J Med, 2011. **364**(9): p. 829-841.
3. Alegre-Diaz, J., et al., *Diabetes and Cause-Specific Mortality in Mexico City.* N Engl J Med, 2016. **375**(20): p. 1961-1971.
4. Gregg, E.W., et al., *Trends in cause-specific mortality among adults with and without diagnosed diabetes in the USA: an epidemiological analysis of linked national survey and vital statistics data.* Lancet, 2018. **391**(10138): p. 2430-2440.
5. Rawshani, A., et al., *Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes.* N Engl J Med, 2017. **376**(15): p. 1407-1418.
6. Saeedi, P., et al., *Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9(th) edition.* Diabetes Res Clin Pract, 2019. **157**: p. 107843.
7. *G. B. D. Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017.* Lancet, 2020. **395**(10225): p. 709-733.
8. *International Agency for the Prevention of Blindness. Vision Atlas - Causes of vision loss*. 2020; Available from: https://www.iapb.org/learn/vision-atlas/causes-of-vision-loss/. (last accessed 07 July 2022)
9. Selvarajah, D., et al., *Diabetic peripheral neuropathy: advances in diagnosis and strategies for screening and early intervention.* Lancet Diabetes Endocrinol, 2019. **7**(12): p. 938-948.
10. Peters, S.A., R.R. Huxley, and M. Woodward, *Sex differences in body anthropometry and composition in individuals with and without diabetes in the UK Biobank.* BMJ Open, 2016. **6**(1): p. e010007.
11. Younossi, Z.M., et al., *The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A systematic review and meta-analysis.* J Hepatol, 2019. **71**(4): p. 793-801.
12. Chatterjee, S., et al., *Type 2 Diabetes as a Risk Factor for Dementia in Women Compared With Men: A Pooled Analysis of 2.3 Million People Comprising More Than 100,000 Cases of Dementia.* Diabetes Care, 2016. **39**(2): p. 300-7.
13. Floud, S., et al., *Body mass index, diet, physical inactivity, and the incidence of dementia in 1 million UK women.* Neurology, 2020. **94**(2): p. e123-e132.
14. Nauck, M.A. and J.J. Meier, *Incretin hormones: Their role in health and disease.* Diabetes Obes Metab, 2018. **20 Suppl 1**: p. 5-21.
15. Scott, R.A., et al., *A genomic approach to therapeutic target validation identifies a glucose-lowering GLP1R variant protective for coronary heart disease.* Sci Transl Med, 2016. **8**(341): p. 341ra76.
16. Pfeffer, M.A., et al., *Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome.* N Engl J Med, 2015. **373**(23): p. 2247-57.
17. Marso, S.P., et al., *Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes.* N Engl J Med, 2016. **375**(4): p. 311-22.
18. Marso, S.P., et al., *Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes.* N Engl J Med, 2016. **375**(19): p. 1834-1844.
19. Holman, R.R., M.A. Bethel, and A.F. Hernandez, *Once-Weekly Exenatide and Cardiovascular Outcomes in Type 2 Diabetes.* N Engl J Med, 2017. **377**(25): p. 2502.

20. Hernandez AF, G.J., Janmohamed S, D'Agostino RB, Granger CG, Jones NP, et al., *Albiglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Cardiovascular Disease.* The Lancet, 2018. **X**(X): p. X.
21. Husain, M., et al., *Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes.* New England Journal of Medicine, 2019. **381**(9): p. 841-851.
22. Gerstein, H.C., et al., *Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial.* Lancet, 2019. **394**(10193): p. 121-130.
23. Gerstein, H.C., et al., *Cardiovascular and Renal Outcomes with Efpeglenatide in Type 2 Diabetes.* N Engl J Med, 2021. **385**(10): p. 896-907.
24. Ruff, C.T., et al., *Subcutaneous infusion of exenatide and cardiovascular outcomes in type 2 diabetes: a non-inferiority randomized controlled trial.* Nat Med, 2022. **28**(1): p. 89-95.
25. Lee, M.M.Y., et al., *Cardiovascular and mortality outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: A meta-analysis with the FREEDOM cardiovascular outcomes trial.* Diabetes Metab Syndr, 2021. **16**(1): p. 102382.
26. Sattar, N., et al., *Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials.* Lancet Diabetes Endocrinol, 2021. **9**(10): p. 653-662.
27. Taylor, S.I., *GLP-1 receptor agonists: differentiation within the class.* Lancet Diabetes Endocrinol, 2018. **6**(2): p. 83-85.
28. Nauck, M.A., et al., *Cardiovascular Actions and Clinical Outcomes With Glucagon-Like Peptide-1 Receptor Agonists and Dipeptidyl Peptidase-4 Inhibitors.* Circulation, 2017. **136**(9): p. 849-870.
29. Mosterd, C.M., P. Bjornstad, and D.H. van Raalte, *Nephroprotective effects of GLP-1 receptor agonists: where do we stand?* J Nephrol, 2020.
30. Khunti, K., et al., *Draft FDA guidance for assessing the safety of glucose lowering therapies: a missed opportunity?* Lancet Diabetes Endocrinol, 2020. **8**(10): p. 810-811.
31. Zelniker, T.A., et al., *SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials.* Lancet, 2019. **393**(10166): p. 31-39.
32. *Food and Drug Administration Center for Drug Evaluation and Research. Type 2 Diabetes Mellitus: Evaluating the Safety of New Drugs for Improving Glycemic Control Guidance for Industry*. 2020; Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/type-2-diabetes-mellitus-evaluating-safety-new-drugs-improving-glycemic-control-guidance-industry. (last accessed 07 July 2022)
33. Cosentino, F., et al., *2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD.* Eur Heart J, 2020. **41**(2): p. 255-323.
34. Datta-Nemdharry, P., et al., *Patterns of anti-diabetic medication use in patients with type 2 diabetes mellitus in England and Wales.* Pharmacoepidemiol Drug Saf, 2017. **26**(2): p. 127-135.
35. Khunti, K., et al., *Patterns of glycaemic control in patients with type 2 diabetes mellitus initiating second-line therapy after metformin monotherapy: Retrospective data for 10 256 individuals from the United Kingdom and Germany.* Diabetes Obes Metab, 2018. **20**(2): p. 389-399.
36. Action to Control Cardiovascular Risk in Diabetes Study, G., et al., *Effects of intensive glucose lowering in type 2 diabetes.* N Engl J Med, 2008. **358**(24): p. 2545-59.

37. Davies, M., et al., *Effect of Oral Semaglutide Compared With Placebo and Subcutaneous Semaglutide on Glycemic Control in Patients With Type 2 Diabetes: A Randomized Clinical Trial.* JAMA, 2017. **318**(15): p. 1460-1470.
38. Pratley, R., et al., *Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial.* Lancet, 2019. **394**(10192): p. 39-50.
39. *ASCEND Collaborative Group. Effects of n−3 Fatty Acid Supplements in Diabetes Mellitus.* New England Journal of Medicine, 2018. **379**(16): p. 1540-1550.
40. *ASCEND Collaborative Group. Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus.* New England Journal of Medicine, 2018. **379**(16): p. 1529-1539.
41. *NHS Digital. National Diabetes Audit, 2017-18 Report 1: Care Processes and Treatment Targets*. 2019; Available from: https://files.digital.nhs.uk/88/F1E544/National%20Diabetes%20Audit%202017-18%20Full%20Report%201%2C%20Care%20Processes%20and%20Treatment%20Targets.pdf. (last accessed 07 July 2022)
42. Peto, R., et al., *Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design.* Br J Cancer, 1976. **34**(6): p. 585-612.
43. Peto, R., et al., *Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. analysis and examples.* Br J Cancer, 1977. **35**(1): p. 1-39.
44. *US Department of Health and Human Services Food and Drug Administration. Guidance for Clinical Investigators, Sponsors, and IRBs. Adverse Event Reporting to IRBs - Improving Human Subject Protection*. 2009; Available from: https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126572.pdf. (last accessed 07 July 2022)
45. *US Department of Health and Human Services Food and Drug Administration. Guidance for Industry. Safety Assessment for IND Safety Reporting*. 2015; Available from: https://www.fda.gov/files/drugs/published/Safety-Assessment-for-IND-Safety-Reporting-Guidance-for-Industry.pdf. (last accessed 07 July 2022)
46. *Expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use . Risk proportionate approaches in clinical trials*. 2017; Available from: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017_04_25_risk_proportionate_approaches_in_ct.pdf. (last accessed 07 July 2022)
47. *European Commision Enterpise and Industry Directorate. Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use*. 2006; Available from: http://www.ceic.pt/documents/20727/20842/Detailed+guidance+on+the+collection%2C+verification+and+presentation+of+adverse+reaction+reports+arising+from+clinical+trials+on+medicinal+products+for+human+use+-+April+2006/4d2233a9-9119-433f-ad2d-52140dcba298. (last accessed 07 July 2022)
48. Meeker-O'Connell, A., et al., *Enhancing clinical evidence by proactively building quality into clinical trials.* Clin Trials, 2016. **13**(4): p. 439-44.
49. Harper, C., et al., *Comparison of the Accuracy and Completeness of Records of Serious Vascular Events in Routinely Collected Data vs Clinical Trial-Adjudicated Direct Follow-up Data in the UK: Secondary Analysis of the ASCEND Randomized Clinical Trial.* JAMA Netw Open, 2021. **4**(12): p. e2139748.
50. *European Medicines Agency. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials*.

2020; Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-sensitivity-analysis-clinical-trials-guideline-statistical-principles_en.pdf. (last accessed 07 July 2022)

6 APPENDICES

6.1 APPENDIX 1: ORGANISATIONAL STRUCTURE AND RESPONSIBILITIES

The University of Oxford will act as sponsor of the trial. Delegation of responsibilities for different aspects of the trial will be set out formally in legal agreements and SOPs.

6.1.1 Principal Investigators

The Principal Investigators (i.e. Chief Investigator and Co-Principal Investigators) have overall responsibility for:

(i) Design and conduct of the Study in collaboration with the Steering Committee;
(ii) Preparation of the Protocol and subsequent revisions;
(iii) Development of SOPs and computer systems;
(iv) Managing the CCO.

6.1.2 Steering Committee

The Steering Committee (see Section 0 for list of members) is responsible for:

(i) Agreement of the final Protocol and the Statistical Analysis Plan;
(ii) Reviewing progress of the study and, if necessary, deciding on Protocol changes;
(iii) Review and approval of study publications (including abstracts, posters, oral presentations and manuscripts), publication proposals and sub-study proposals;
(iv) Reviewing new studies that may be of relevance.

6.1.3 Data Monitoring Committee

The independent DMC is responsible for:

(i) Reviewing unblinded interim analyses according to the schedule in the Protocol;
(ii) Advising the Steering Committee if, in its view, the randomised data provide evidence that may warrant early termination for either efficacy or safety.

6.1.4 Central Coordinating Office

The CCO is responsible for the overall coordination of the Study, including:

(i) Study planning and organisation of Steering Committee meetings;
(ii) Ensuring necessary regulatory approvals (in collaboration with Novo Nordisk);
(iii) Obtaining central Ethics Committee approval;
(iv) Design, implementation and maintenance of IT systems for the study;
(v) Logging and processing responses from patients who respond to an invitation to join the trial;
(vi) Training study staff;
(vii) Monitoring overall progress of the study, and overall budget management;
(viii) Managing the flagging of participants, and the receipt and secure storage of linked NHS data;
(ix) Provision of study materials, and ensuring adequate study drug supply in liaison with Novo Nordisk;
(x) Expedited reporting of SUSARs to regulatory authorities;
(xi) Preparation of the trial-specific DSUR;
(xii) Clinical safety monitoring and reporting of SARs to Novo Nordisk;
(xiii) Clinical oversight for study participants;
(xiv) Dealing with enquiries from participants and others;

(xv) Distribution of packs of study treatment to trial participants;
(xvi) Ensure that the study is conducted according to the protocol.

6.1.5 Local sites

(i) Identifying an investigator to oversee the activities of staff at the collaborating institution (this could be a clinician or senior nurse or other healthcare professional);
(ii) Identifying research coordinators to support the study;
(iii) Conducting telephone or video calls with study participants as directed by the CCO.

6.1.6 Novo Nordisk

Novo Nordisk is responsible for

(i) Funding the trial;
(ii) Supply, packaging and provision of study drug to the UK-based contract distributer (in liaison with the CCO);
(iii) Routine pharmacovigilance for oral semaglutide;
(iv) Reviewing and agreeing the trial Protocol with the Principal Investigators.

6.2 APPENDIX 2: ESTIMANDS

6.2.1 Estimand of the primary outcome

The treatment effect of oral semaglutide once-daily vs placebo, both added to standard of care, on the primary outcome will be estimated for the primary assessment. The treatment effect of interest is a comparison of two treatment regimens; one where oral semaglutide is available and another where it is not, irrespective of treatment discontinuation for any reason and changes to cardiovascular risk lowering background medication while the patient is alive, conditional on the baseline covariates used in minimised randomisation.

In detail, the primary estimand is defined with the five attributes as described in ICH E9(R1) addendum [50]:

- Treatment condition: The treatment regimen evaluated is oral semaglutide once-daily vs placebo, both added to standard of care, irrespective of treatment discontinuation for any reason and changes to CV risk lowering background medication, i.e. handled by the treatment policy strategy.
- Population: The treatment effect is assessed for the target population as defined by the protocol inclusion/exclusion criteria for patients who adhere to the pre-specified run-in period.
- Variable: The treatment effect is assessed by time to first occurrence of the primary endpoint, observed from randomisation to end-of-trial.
- Remaining intercurrent events: Causes of death not part of the variable (endpoint) are handled by the while-alive strategy. Other intercurrent events are addressed in the treatment condition attribute.
- Population-level summary: The ratio of the primary endpoint event rate (hazard ratio) between oral semaglutide once-daily and placebo.

6.2.2 Estimand for the secondary outcome

The treatment effect of oral semaglutide once-daily vs placebo, both added to standard of care, on the secondary outcome will be estimated for the secondary assessment. The treatment effect of interest is a comparison of two treatment regimens; one where oral semaglutide is available and another where it is not, irrespective of adherence to randomised treatment and changes to cardiovascular risk lowering background medication, while the patient is alive, conditional on the baseline covariates used in minimised randomisation [50].

6.2.3 Estimand for the tertiary outcomes

The treatment effect of oral semaglutide once-daily vs placebo, both added to standard of care, on the tertiary outcomes will be estimated for the tertiary assessments. As for primary and secondary outcomes the treatment effect of interest is a comparison of two treatment regimens; one where oral semaglutide is available and another where it is not, irrespective of adherence to randomised treatment and changes to cardiovascular risk lowering background medication, while the patient is alive, conditional on the baseline covariates used in minimised randomisation [50].

6.3 APPENDIX 3: ASSESSMENT SCHEDULE AND PROCEDURES

Task	Activity	Registration	Screening Assessment	Randomisation Assessment	Follow-up assessments requested at 12 and 24 weeks, then at 24 week intervals	Final Follow-up assessment
Demographics	Contact details	✓	✓	✓	✓	✓
Consent	Record informed consent		✓			
	Confirm consent			✓		
Eligibility and medical history	Medical history		✓	✓		
	Smoking and alcohol			✓		
	Use of insulin		✓	✓	✓	✓
Height and weight	Self-reported height and weight			✓		
Investigator approval*	Entry into run-in		✓			
Letter to General Practitioner*	Entry into run-in		✓			
	Confirming randomisation			✓		
Questionnaires/ surveys	EQ-5D questionnaire			✓		✓
	VR-12				✓‡	
	PAID scale				✓†	
Randomisation*				✓		
Mail-out of study treatment*	Run-in treatment		✓			
	Randomised study treatment			✓	✓	
Adverse events and pre-specified outcomes	Reasons for stopping treatment			✓	✓	✓
	Selected study outcomes			✓	✓	✓
	Linkage to NHS datasets		Regular extracts of linked routine health care and registry data throughout the trial			

*these tasks occur shortly after the completion of the relevant assessment
‡ early during the scheduled treatment period (1-2 years after randomisation) and again later in the scheduled treatment period (3-4 years after randomisation)
† later in the scheduled treatment period (3-4 years after randomisation)

6.4 APPENDIX 4: ASCEND PLUS STUDY TEAM

6.4.1 Steering Committee

(Major organisational and policy decisions, and scientific advice; blinded to treatment allocation)

Chair	Professor Louise Bowman	CTSU, University of Oxford, UK
Vice Chairs	Professor Isla MacKenzie	University of Dundee, UK
	Associate Professor Richard Bulbulia	CTSU, University of Oxford, UK
Lead Investigators	Professor David Preiss (Chief/Principal Investigator)	CTSU, University of Oxford, UK
	Associate Professor Marion Mafham (Co-Principal Investigator)	CTSU, University of Oxford, UK
	Dr Rohan Wijesurendra (Clinical Coordinator)	CTSU, University of Oxford, UK
Statistician	Dr Natalie Staplin	CTSU, University of Oxford, UK
Data Linkage Lead	Dr Charlie Harper	CTSU, University of Oxford, UK
Lay members	Ms Susan Dickie	
	Mr John Roberts	
Other members	Professor Amanda Adler	Diabetes Trials Unit, University of Oxford, UK
	Professor Steve Bain	University of Swansea, UK
	Professor Melanie Davies	University of Leicester, UK
	Professor Kamlesh Khunti	University of Leicester, UK
	Professor Nick Mills	University of Edinburgh, UK
	Dr Rustam Rea	Oxford University Hospitals NHS Foundation Trust, UK
Novo Nordisk	Four members from Novo Nordisk (details provided in the Steering Committee Charter)	Novo Nordisk

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Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF, UK
Tel: +44(0)1865 287700; Email: ascend-plus@ndph.ox.ac.uk; Website: www.ascend-plus-trial.org

6.5 APPENDIX 5: DETAILS OF APPROVED SUB-STUDIES

ASCEND PLUS sub-studies must have approval from the Trial Steering Committee (see Section 2.7.4.6) and, where appropriate, a favourable opinion from the Research Ethics Committee and any other required approvals (e.g. MHRA or Confidentiality Advisory Group). An outline of each sub-study is provided in this section with further details provided within the relevant sub-study protocol.

6.5.1 ASCEND PLUS sub-study: Impact of behavioural nudges on response to invitation

Title:	Impact of behavioural nudges on response to invitation
Sub-study aims:	To assess whether the use of specifically developed wording in invitation letters (behavioural nudges) can positively influence people to consider joining the study and to take part in ASCEND PLUS
Sub-study eligibility:	Patients who are invited to join ASCEND PLUS
Intervention:	The sub-study will randomise invited patients to receive one of (i) a control invitation letter (ii) an invitation letter with an altruism behavioural nudge (iii) an invitation letter with an individualism and norms behavioural nudge
Sub-study size:	Approximately 180,000 patients considered potentially eligible to join the ASCEND PLUS trial who are mailed an invitation, consisting of ~60,000 mailed a control letter, ~60,000 mailed a letter with an altruism behavioural nudge and ~60,000 mailed a letter with an individualism and norms behavioural nudge
Outcomes:	Sub-study primary outcome: Number of patients returning the invitation letter reply form indicating positive interest in joining the trial Sub-study secondary outcomes: (i) Number of participants entering run-in, (ii) Number of participants randomised
Sub-study protocol:	ASCEND PLUS sub-study: Impact of behavioural nudges on response to invitation sub-study protocol EDMS #8215
Collaborators:	NHS DigiTrials at NHS England

6.6 APPENDIX 6: DETAILS OF ADDITIONAL EVALUATIONS WITHIN ASCEND PLUS

This section provides details of additional evaluations that are to be investigated within the ASCEND PLUS trial. Any additional evaluations must have the support of the trial Steering Committee and approval from the REC, MHRA and the Confidentiality Advisory Group, as appropriate.

6.6.1 Evaluation of the ethics of informed consent in the ASCEND PLUS trial

6.6.1.1 Ethics of informed consent evaluation: Background and rationale

The ASCEND PLUS design offers potential participants a choice of informed consent method; either an eligibility discussion with a research nurse via telephone or video call (followed by mailed or online consent), or self-directed online consent preceded by an online screening questionnaire (i.e. e-consent). The use of e-consent in clinical trials to date is uncommon and there is a lack of well conducted research evaluating the ethics of seeking consent using electronic methods. It was agreed with the REC during the initial review and approval of ASCEND PLUS that such an evaluation would be undertaken within the study in collaboration with the Ethox Centre at the University of Oxford.

6.6.1.2 Objectives of the ethics of informed consent evaluation

The primary objectives of this evaluation are:

- To explore and understand patient and study staff experiences of the ASCEND PLUS recruitment process (choice of self-directed electronic consent [with/without phone/video support] or phone/video);
- To engage participants in ethical reasoning about the various parts of the recruitment process – how acceptable they found it in their own experience, options they didn't take, and what reasons underpin their views.

Secondary objectives include:

- To analyse ethical challenges to the concept of electronic consent in CTIMPs;
- To consider the ethical justification for using e-consent processes wholly or partially in CTIMPs.

6.6.1.3 Methodology and sampling strategy for the ethics of informed consent evaluation

Semi-structured interviews will be undertaken with the following groups to explore their choices and experiences within the ASCEND PLUS recruitment process.

- ASCEND PLUS participants who completed the informed consent process and individuals who responded positively to a study invitation and commenced, but did not complete the screening process (referred to as 'patient ethics evaluation participants')
- Study staff involved in the ASCEND PLUS recruitment process (referred to as 'staff ethics evaluation participants').

The interview structure will broadly be:

1. Participants' and stakeholders' experiences and recall of the recruitment process; what they thought about the electronic components if they chose a purely or mixed electronic process

2. A refresher description (from interviewers) of the recruitment processes available, the electronic components and how they aim to meet regulatory and ethical considerations
3. Participants' and stakeholders' perceptions of the advantages and disadvantages of electronic components within the recruitment process; acceptability of the process

As part of point 3 above, individuals participating in the ethics evaluation will be encouraged to engage in ethical reasoning about the recruitment process – how acceptable they found it, and what reasons underpin their views.

Potential patient ethics evaluation participants will be purposively sampled using the ASCEND PLUS databases to invite a representative sample who have taken a range of different approaches to the e-consent process in the ASCEND PLUS study. They include those who pursued (i) the self-screening option, (ii) the nurse-screening option or (iii) a combination of the two. In each of the three groups, some will have given consent, and some will have completed only part of the process.

Staff involved in the ASCEND PLUS recruitment process will be purposively sampled from the trial database (including staff role, location and dates of completion of relevant study activities) to ensure that individuals with a broad range of experience within the trial are invited, for example people working at the University of Oxford and at local research sites. The sampling will include staff with a range of roles within the study (including trial monitors, clinical staff, research nurses completing the screening and consent assessments and study administrators). Invitations will be limited to people currently working on the trial.

Individuals who express an interest in taking part in the ethics of informed consent evaluation will be sent an information sheet that contains an explanation of the verbal consent process for the additional evaluation (i.e. the points of agreement that they will be asked to provide when they commence the structured interview) either electronically or in hard copy. Potential staff ethics evaluation participants will receive an invitation letter by e-mail.

6.6.1.4 Invitation and consent for the ethics of informed consent evaluation

Potential patient ethics evaluation participants will be sent an invitation letter by post or e-mail asking them to take part in the additional evaluation. They will be asked to indicate willingness to take part by return email, or by filling in and returning a reply slip in a stamped addressed envelope provided. Approximately two weeks later, the ASCEND PLUS team will contact the individual by telephone, e-mail or letter to answer any questions about the additional evaluation and arrange a time for the structured interview. The interviews will be primarily conducted by video or telephone call. Should any individual wish to be interviewed in person, the interviews will be held at the ASCEND PLUS Coordinating Centre in Oxford and reasonable travel expenses provided. Potential staff ethics evaluation participants will be sent an invitation e-mail asking them to send an e-mail reply if they are interested in taking part in the ethics interview.

At the start of the structured interview, verbal consent (or written consent if the interview is conducted in person) for the additional evaluation will be sought. The person who obtains this consent will be suitably qualified and experienced, and have been authorised to do so by the Chief Investigator. If the interview is conducted by video call, the researcher will have a verbal consent form with points of consent. They will read out each point and seek verbal agreement from the participant. The researcher will confirm whether participant wishes to go ahead with evaluation and will sign a paper consent form. The individual taking part in the ethics evaluation will be sent a copy of the points to which they verbally

agreed. If the interview is conducted in person, written informed consent will be sought from the participant.

During the course of the evaluation a participant may choose to withdraw from commencing or continuing with an interview or from use of their interview data.

The interview will take about an hour and will be recorded using the audio record function on appropriate video-conferencing software or an audiotape in the case of in-person interviews. Transcriptions will be done by a University of Oxford approved provider. The audio files provided to any external provider will be identified using a unique ID only. Interview data will be entered on the qualitative data management and analysis software NVIVO. The paper consent forms, voice recordings and interview transcripts will be retained centrally as source documents according to the ASCEND PLUS study data management procedures.

6.6.1.5 Analysis plan and anticipated sample size for the ethics of informed consent evaluation

This qualitative interview evaluation will use thematic analysis to analyse the data. In order to ensure that the themes developed within the analysis process capture the data in their entirety, the constant comparative method developed within grounded theory will be adopted. Strategies of open coding and thematic mapping will be adopted to ensure that the themes developed accurately reflect the range of different meanings evident in the data set.

It is anticipated that approximately 50 individuals will be interviewed subject to data saturation. Data saturation is the point at which no new themes are emerging from the data analysis and further recruitment would not add to the themes arising and conclusions being drawn.