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ASCEND PLUS - a research study to test whether a treatment called oral semaglutide can protect people with type 2 diabetes from heart attacks, strokes, and other health problems

Submission date	Recruitment status	[X] Prospectively registered
21/04/2022	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
27/06/2022	Ongoing	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
16/03/2023	Nutritional, Metabolic, Endocrine	[ ] Record updated in last year

Plain English summary of protocol

Background and study aims

This trial is called ASCEND PLUS. It is testing whether, for people with type 2 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.

Oral semaglutide helps to control blood sugar levels and lower body weight, and is already approved for use in the UK as a treatment for some patients with type 2 diabetes.

Who can participate?

The study will involve 20,000 volunteers with type 2 diabetes aged at least 55 years who have not had a heart attack or stroke in the past.

Potentially eligible participants will be identified by an automated electronic search of coded medical records held by NHS Digital (England). The trial will commence in England and the study team will subsequently seek the relevant permissions to also run the trial in Wales and Scotland.

What does the study involve?

Each participant will be asked to take one study tablet each day for about 5 years and to complete a total of about 12 questionnaires during this time.

Half of the study participants will get tablets containing semaglutide and half will get inactive placebo tablets (which look like the oral semaglutide but have no active drug in them). Which treatment a participant gets is decided by chance and the participant will not know if they are taking the active tablet. No clinic visits are required as part of this study. The study medication will be sent to each participant's address by post.

What are the possible benefits and risks of participating?
The health of participants may or may not improve as a result of taking part in the trial. If the trial shows benefit, this will help to prevent many patients with type 2 diabetes from suffering heart attacks, strokes and other vascular problems in the future.

Oral semaglutide is approved in the UK for treating type 2 diabetes. Most people treated with oral semaglutide do not have any side effects, but about one in ten people who take the tablets experience nausea (feeling sick), vomiting, or diarrhoea. If severe, these symptoms may occasionally result in dehydration. These problems usually happen soon after starting the medication (or when the dose is increased) and go away with time. Most people who develop these symptoms do manage to continue taking oral semaglutide.

Oral semaglutide may rapidly improve blood sugar levels. Good blood sugar control helps to protect against eye disease caused by diabetes in the longer term, but fast improvements in blood sugar control may lead to a temporary worsening of diabetic eye disease in some patients. It is therefore important that participants attend their NHS retinal screening appointments as part of their regular diabetes care.

Women who are pregnant, planning a pregnancy or breastfeeding will be excluded from the trial because oral semaglutide is not recommended during pregnancy or breastfeeding.

Participants who take insulin or a sulphonylurea might experience hypoglycaemia (low blood sugar or 'hypo') when starting taking semaglutide. It is therefore important for participants who already monitor blood sugar levels at home to continue to do this regularly.

Where is the study run from?
University of Oxford (UK)

When is the study starting and how long is it expected to run for?
March 2022 to August 2048

Who is funding the study?
Novo Nordisk (Denmark)

Who is the main contact?
Ryonfa Lee, ascend-plus@ndph.ox.ac.uk

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Additional identifiers

EudraCT/CTIS number
2021-003792-33

IRAS number
1004252

ClinicalTrials.gov number
NCT05441267

Secondary identifying numbers
CTSU_ASCEND-PLUS, IRAS 1004252, CPMS 51088, U1111-1284-0262

Study information

Scientific Title
A Study of Cardiovascular Events iN Diabetes Plus (ASCEND PLUS)

Acronym
ASCEND PLUS

Study objectives
The main aim of the study is to find out whether regularly taking a treatment called oral semaglutide can reduce the risk of people aged 55 or over, living with type 2 diabetes, from suffering a first heart attack, stroke, mini-stroke (known as a 'transient ischaemic attack), a heart artery balloon/stent procedure or of dying because of vascular problems.

A secondary aim is to investigate whether regularly taking oral semaglutide can reduce the risk of suffering a first heart attack or stroke, or of dying from circulatory disease. The trial will also test whether the treatment reduces other complications of diabetes such as chronic kidney disease, the need to start insulin, low blood sugar (hypoglycaemia), health problems related to weight, and dementia.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 19/05/2022, South Central - Oxford B Research Ethics Committee (Ground Floor, Temple Quay House, 2 The Square, Bristol, United Kingdom, BS1 6PN; +44 207 104 8360; oxfordb.rec@hra.nhs.uk), ref: 22/SC/0116

Study design
Interventional double blind randomized parallel group placebo controlled trial

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Community

Study type(s)
Treatment

Participant information sheet

Health condition(s) or problem(s) studied
Type 2 diabetes. The most common type of diabetes - a disease that occurs when your blood glucose (also called blood sugar) is too high.

Interventions

Eligible participants will initially enter an active run-in phase during which they will be asked to take one tablet daily of oral semaglutide 3mg for 4 weeks, followed by oral semaglutide 7mg for 4-8 weeks. Participants who remain eligible with then be randomised, by computer using minimisation, to receive either oral semaglutide or placebo during the scheduled treatment period. They will be provided with either oral semaglutide 14mg or placebo, to be taken as one tablet daily. Participants will have the opportunity to reduce the dose of study treatment to 7mg one tablet daily or placebo if necessary.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
oral semaglutide

Primary outcome measure
Time to first occurrence of the expanded composite of major adverse cardiovascular events (MACE+), defined as:
1. Death from cardiovascular disease
2. Non-fatal myocardial infarction
3. Non-fatal stroke
4. Transient ischaemic attack
5. Coronary revascularisation

Follow-up of all randomised participants is scheduled to continue until the required number of participants has experienced a primary outcome following randomization. This is expected to occur when average follow up duration is approximately 5 years. Pre-specified outcomes and serious adverse events will be identified by regular linkage to NHS records, supplemented by seeking information from participants for certain events during follow-up assessments (conducted at six-monthly intervals).

Secondary outcome measures
Time to first occurrence of the composite of major cardiovascular events (MACE), defined as:
1. Death from cardiovascular disease
2. Non-fatal myocardial infarction
3. Non-fatal stroke

Follow-up of all randomised participants is scheduled to continue until the required number of participants has experienced a primary outcome following randomization. This is expected to occur when average follow up duration is approximately 5 years. Pre-specified outcomes and serious adverse events will be identified by regular linkage to NHS records, supplemented by seeking information from participants for certain events during follow-up assessments (conducted at six-monthly intervals).

Overall study start date
21/03/2022

Completion date
17/08/2048

Eligibility

Key inclusion criteria
1. Adults aged at least 55 years
2. Type 2 diabetes mellitus

Participant type(s)
Patient

Age group
Adult

Lower age limit
55 Years

Sex
Both

Target number of participants
20000

Key exclusion criteria
1. Myocardial Infarction
2. Stroke
3. Current or planned treatment with a GLP-1 RA
4. Previous hypersensitivity to or intolerance of GLP-1 RA therapy
5. Severe hypoglycaemia within the last six months or during run-in
6. Symptomatic hypoglycaemia within the last month
7. Currently under consideration to commence insulin
8. Severe heart failure (NYHA class 4)
9. Current or planned renal replacement therapy
10. Unwilling to complete regular follow-up assessments
11. Ongoing treatment for cancer or diagnosis with cancer (excluding non-melanoma skin cancer) in the last 2 years
12. Type 1 or other type of diabetes (e.g. MODY)
13. History of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma
14. Currently breastfeeding or pregnant, or planning a pregnancy
15. Any serious illness which is likely to limit survival or active participation for at least 5 years
16. Current participation in a clinical trial with an unlicensed investigational medicinal product used to treat diabetes
17. 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
18. Non-adherence to run-in treatment (i.e. reports taking the run-in tablets ‘Never’ or ‘Only occasionally’
19. Their doctor does not wish them to be randomised

Date of first enrolment
13/03/2023

Date of final enrolment

01/09/2024

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
ASCEND PLUS Coordinating Office
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ROR
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Funder(s)

Funder type
Industry

Funder Name
Novo Nordisk

Alternative Name(s)
Novo Nordisk Global

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
Denmark

Results and Publications

Publication and dissemination plan
Peer reviewed scientific journals
Internal report
Conference presentation
Publication on website
Submission to regulatory authorities

Intention to publish date
17/05/2029

Individual participant data (IPD) sharing plan
Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators.
In line with the Nuffield Department of Population Health's policy and the study protocol, proposals to share study data will be reviewed by the Steering Committee, and approval will not be unreasonably withheld. 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.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No