ISRCTN71283871 https://doi.org/10.1186/ISRCTN71283871

Does semaglutide change the build up of Alzheimer's disease proteins in people at risk?

Submission date
21/01/2022

Recruitment status
No longer recruiting

Registration date
02/02/2022

Overall study status
Ongoing

Last Edited
25/06/2024

Condition category
Nervous System Diseases

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
The lack of effective treatments for dementia remains one of the key challenges to modern medicine and society. Its leading cause is Alzheimer’s disease (AD), a condition where proteins (called amyloid and tau) build up in the brain causing inflammation and loss of nerve cells. This process begins decades before the first symptoms of dementia appear, offering an opportunity to stop it in its tracks with the right treatment.
Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are a class of medication used to treat type 2 diabetes and obesity. They have been shown to reduce the risk of heart attack, stroke, and kidney disease in people with diabetes, and in animal experiments, they have also been found to affect the mechanisms thought to be involved in AD.
This study aims to examine the effects of semaglutide (a GLP-1 RA tablet) on the build-up of AD proteins, brain inflammation and thinking ability in people thought to be at high risk of developing AD.

Who can participate?
Men and women aged 55 years and above who do not have dementia and have evidence for a build-up of the amyloid protein in their brains.

What does the study involve?
The study will involve taking a tablet called semaglutide or a placebo (dummy drug). The researchers will conduct several tests over a year to assess the effect of the drug on the risk of Alzheimer's, most notably a head scan to detect the amount of a protein called tau, to see whether those given semaglutide tablets do better compared with those given dummy tablets.

What are the possible benefits and risks of participating?
While there are no immediate benefits for those participating in the study, it is hoped that this research will lead to potential new treatment for AD for which there is currently no effective treatment. While semaglutide is a safe drug, it does carry the risk of side effects like any other medication.

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 2021 to March 2026

Who is funding the study?
Novo Nordisk (Denmark)

Who is the main contact?
Hannah Bass
hannah.bass@psych.ox.ac.uk

Study website
https://www.rdm.ox.ac.uk/dtu

Contact information

Type(s)
Principal Investigator

Contact name
Dr Ivan Koychev

Contact details
Department of Psychiatry
Warneford Hospital
Oxford
United Kingdom
OX3 7GB

Type(s)
Public

Contact name
Ms Hannah Bass

Contact details
Department of Psychiatry
University of Oxford
Oxford
United Kingdom
OX3 7JX
+44 (0)1865 618291
hannah.bass@psych.ox.ac.uk

Additional identifiers

EudraCT/CTIS number
2021-003328-34

IRAS number
300550

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
NN6535-4887, IRAS 300550

Study information

Scientific Title
Impact of semaglutide in amyloid positivity

Acronym
ISAP

Study objectives
To explore possible mechanisms underlying the potential disease modifying effects of semaglutide, a glucagon-like peptide-1 receptor agonist in a group of individuals with preclinical or prodromal Alzheimer’s disease.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved, West Midland – Edgbaston Research Ethics Committee (3rd Floor Barlow House, Minshull Street, Manchester, M1 3DZ, UK; +44 (0)207 104 8155, +44 (0)207 104 8357; edgbaston.rec@hra.nhs.uk), ref: NSA 04

Study design
Double-blind randomized parallel-group placebo-controlled superiority trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Prevention

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Alzheimer's disease

Interventions
Intervention: Semaglutide 3, 7 and 14 mg tablets, titrated to 14 mg once daily, oral
Comparator: Matching placebo, once-daily, oral

The total duration of treatment is 52 weeks for both arms; follow-up is 5 to 6 weeks following treatment completion.

At their randomisation visit, study participants who fulfil all the inclusion criteria and violate none of the exclusion criteria will be assigned a unique randomisation number. Randomisation numbers will be allocated to eligible participants by the ISAP EDC to assign semaglutide or matching placebo in an overall 1:1 ratio. This assignment will be performed using a computerised procedure with minimisation (adaptive stratified sampling) based on T2DM (Yes /No), MCI (Yes/No) and trial site to maintain balance between treatment groups. No participant replacement will be allowed.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Semaglutide

Primary outcome measure
Current primary outcome measure as of 01/05/2024:
The primary endpoint is the annualised change in cortical tau. It is measured at baseline and 52-week visits using PET tau and expressed in standardised uptake value ratio (SUVR).

Previous primary outcome measure:
Tau cortical standardized uptake value ratio (SUVR) measured using positron emission tomography (PET) at baseline and following treatment at week 52 (visit 7)

Secondary outcome measures
Current secondary outcome measures as of 01/05/2024:
1. Cortical neuroinflammatory signal measured using translocator protein (TSPO) PET SUVR at baseline and 52 weeks
2. Plasma biomarkers of neuroinflammation measured by estimating plasma glial fibrillary acidic protein (GFAP) protein levels at screening, baseline, weeks 4, 8, 26, 39 and 52
3. Plasma AD biomarkers: p-tau181 levels and Aβ42/40 ratio at screening, baseline, weeks 4, 8, 26, 39 and 52
4. Cognition measured in-clinic with pen and paper cognitive test (Addenbrooke's Cognitive Assessment [ACE-III]) scores at baseline, weeks 26 and 52 as well as computerised in-clinic cognitive battery (CANTAB) at baseline, weeks 26 and 52. Cognition is also measured remotely through a browser-based cognitive battery (Cognitron) 1 at baseline, weeks 26 and 52
5. Presence of Adverse Events (AEs), Serious Adverse Events (SAEs), Adverse Reactions (ARs), Serious Adverse Reactions (SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs). Information on those is collected through interviews at baseline, weeks 4, 8, 26, 39, 52 and follow-up call
6. Neurodegeneration measured by determination of hippocampal volume using structural MRI at baseline and 52 weeks as well as plasma levels of neurofilament light (NFL) measured at

screening, baseline, weeks 4, 8, 26, 39 and 52
7. Depression and anxiety scores measured by the Center for Epidemiologic Studies Depression Scale (CES-D) and Health Anxiety Inventory (HAI) scales at baseline and 52 weeks
8. Levels of distress at AD risk disclosure measured through the Impact of Genetic Testing for Alzheimer's disease scale at weeks 26 and 52
9. Quality of life measured by EQ-5D-5L scales at baseline and 52 weeks
10. Level and pattern of physical activity and circadian rhythms measured using wrist-worn actigraphy at baseline and 52 weeks

Previous secondary outcome measures:
1. Neuroinflammation measured using Translocator protein (TSPO) PET SUVR, plasma glial fibrillary acidic protein (GFAP) protein level at Baseline & week 52 for TSPO PET; Screening, baseline, weeks 4, 8, 26, 39 & 52 for GFAP
2. AD blood biomarkers measured using AD plasma biomarkers (p-tau181, Aβ42/40) at Screening, baseline, weeks 4, 8, 26, 39 & 52
3. Cognition measured using the Pen and paper cognitive test (ACE-III), Computerised in-clinic cognitive battery (CANTAB): Performance and speech-derived metrics and the Remote cognitive battery (Cognitron) at Baseline, weeks 26 & 52
4. Safety measured using Adverse Event reports at Baseline, week 4, 8, 26, 39, 52 and follow-up call
5. Neurodegeneration measured using Hippocampal volume (MRI), plasma neurofilament light (NFL) at Baseline & week 52 MRI; Screening, baseline, weeks 4, 8, 26, 39 & 52 NFL
6. Quality of life measured using the EuroQol EQ-5D-5L scale at Baseline & week 52
7. Physical activity and circadian rhythms measured using a Wrist-worn actigraphy at Baseline & week 52

Overall study start date
01/03/2021

Completion date
15/03/2026

Eligibility

Key inclusion criteria
1. Participant is willing and able to give informed consent for participation in the trial
2. Male or female, aged 55 years or above
3. Amyloid-positivity as evidenced by PET
4. Fluent English speaker, as assessed by the Investigator
5. In the Investigator’s opinion, is able and willing to comply with all trial requirements
6. Willing to allow his or her General Practitioner (GP), if appropriate, to be notified of participation in the trial
7. Clinical dementia rating (CDR) of 0.5 or below.
8. An informant that is available to the research team for the purposes of CDR scoring

Participant type(s)
Other

Age group
Adult

Lower age limit
55 Years

Sex
Both

Target number of participants
88

Key exclusion criteria
1. Diagnosis of dementia
2. Treatment with a GLP-1 RA: current or in the past 6 months
3. Women who are pregnant, breastfeeding or of childbearing potential (see Appendix D for definition)
4. People with type 1 diabetes mellitus, secondary diabetes, or maturity-onset diabetes of the young (MODY)
5. People with T2DM who have pre-proliferative or proliferative diabetic retinopathy, or diabetic maculopathy
6. People with T2DM if the cap of 30% of participants with T2DM randomised has been met
7. Poorly controlled T2DM, defined as HbA1c ≥10% (86 mmol/mol)
8. Evidence of severe renal impairment or an estimated glomerular filtration rate (eGFR) derived from serum creatinine (using the simple CKD-EPI formula) of <30 ml/min/1.73 m^2
9. Evidence of hepatic cirrhosis as assessed by medical history
10. A psychiatric condition which in the opinion of the investigator may affect the safety of the participant or the outcomes of the study.
11. Any contraindication for MRI or PET scans, including but not limited to: MR-incompatible pacemakers, pregnancy, aneurysm clip, implanted neural stimulator, implanted cardiac pacemaker or auto-defibrillator, cochlear implant, ocular foreign body, recent carotid stent, CSF shunt, other implanted medical device, e.g., Swan Ganz catheter, insulin pump, as assessed by a standard pre-MRI questionnaire
12. Participant with a life expectancy of fewer than 6 months
13. Currently enrolled in another investigational device or drug study, or less than 30 days between randomisation and ending another investigational device or drug study or receiving other investigational treatment(s). Patients participating in a purely observational trial will not be excluded
14. Presence or history of malignant neoplasm (other than basal or squamous cell skin cancer, in-situ carcinomas of the cervix, or in situ prostate cancer) within 5 years prior to the day of screening
15. Lack of access to a suitable digital technology to allow remote cognitive testing (PC or tablet connected to the internet)
16. Significant eye or hearing impairment that in the opinion of the investigator may affect study procedures
17. People with the low-affinity binding variant of the rs6971 allele of the TSPO gene
18. Known or suspected hypersensitivity to the trial product or related products
19. Poor venous access or other contraindications that would make blood sampling difficult
20. Participant that in the view of the investigator will experience significant distress in the event of a positive amyloid status disclosure. Such individuals will not undergo amyloid screening
21. Diabetic individuals treated with sulphonylureas or insulin where dose adjustment as described in protocol is not possible for whatever reason
22. Individuals with significant radiation exposure in the past year for whom in the opinion of the investigator the additional exposure will result in an unacceptable risk

Date of first enrolment
15/08/2022

Date of final enrolment
15/11/2024

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
NIHR Oxford Cognitive Health Clinical Research Facility
Warneford Hospital
Warneford Lane
Oxford
United Kingdom
OX3 7JX

Study participating centre
Royal Devon University Healthcare NHS Foundation Trust
Royal Devon University NHS Ft
Barrack Road
Exeter
United Kingdom
EX2 5DW

Study participating centre
Imperial College Healthcare NHS Trust
The Bays
St Marys Hospital
South Wharf Road
London
United Kingdom
W2 1NY

Study participating centre
University College London Hospitals
Dementia Research Centre
First Floor
8-11 Queen Square

London
United Kingdom
WC1N 3BG

Study participating centre
North Bristol NHS Trust
Trust Headquarters
Southmead Hospital
Southmead Road
Westbury-on-Trym
Bristol
United Kingdom
BS10 5NB

Study participating centre
Cambridgeshire and Peterborough NHS Foundation Trust
Elizabeth House,
Fulbourn Hospital
Fulbourn
Cambridge
United Kingdom
CB21 5EF

Sponsor information

Organisation
University of Oxford

Sponsor details
Boundary Brook House
Churchill Drive
Headington
Oxford
England
United Kingdom
OX3 7GB
+44 (0)1865 289886
RGEA.sponsor@admin.ox.ac.uk

Sponsor type
University/education

Website

https://www.ox.ac.uk/

ROR
https://ror.org/052gg0110

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
The Steering Committee will recommend a writing group for each manuscript with a lead author and approve the production of all ISAP trial manuscripts. Writing groups will comprise typically of three to seven individuals identified usually from trial members. The lead author will be responsible for ensuring that the paper is written in a timely manner, liaising with the trial statistician as necessary, and keeping the ISAP Trial Manager informed of progress. For papers involving analysis of data generated by the ISAP Trial, at least one member of the writing group will be from the MRC Biostatistics Unit.
Major publications will be authored “on behalf of the ISAP Trial group” and produced in accordance with CONSORT guidelines. The first substantive publication will list all trial staff and committee members. Individual authorship will be governed by the international standards for the publication of academic research. The Trial Steering Committee (TSC) will review and comment on drafts of papers to ensure accurate, uniform, timely and high-quality reporting of the ISAP trial and will be responsible for the final approval and submission of all ISAP publications.

Intention to publish date
01/03/2025

Individual participant data (IPD) sharing plan

Current IPD sharing plan as of 25/07/2023:
Requests for access to ISAP data should be submitted to the Trial Steering Committee. Contact details and information will be available at: https://www.rdm.ox.ac.uk/about/our-clinical-facilities-and-mrc-units/DTU/diabetes-trial-unit

Previous IPD sharing plan:
Requests for access to ISAP data should be submitted to the Trial Steering Committee. Contact details and information will be available at: https://www.dtu.ox.ac.uk/ISAP/.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		25/06/2024	25/06/2024	Yes	No