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RESILIENT

Submission date	Recruitment status	[_] Prospectively registered
09/10/2017	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
25/01/2018	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
14/02/2024	Nutritional, Metabolic, Endocrine	[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Type 2 diabetes mellitus is a long term disorder that causes the body to not be able to control the sugar level in the blood. Obesity is a major risk factor for diabetes. Some treatments for diabetes can cause patients to put on weight but newer treatments for diabetes target weight loss in addition to improving blood glucose control. There have been two new promising medications available for treating Type 2 diabetes: the GLP-1 receptor agonist and the SGLT2 inhibitor. Both are associated with significant improvement in blood glucose levels and in body weight. To date there is no evidence about using these two drugs together even though we think there are good reasons to do this. We think that if we use these medications together they will complement each other improving weight loss and blood glucose control. This study aims to assess mechanistic effects of combination therapy of dapagliflozin with exenatide QW versus dapagliflozin alone in obese (BMI>30 kg/m2) patients with Type 2 diabetes mellitus.

Who can participate?
Adults aged 18 to 65 years old who have been diagnoses with type 2 diabetes.

What does the study involve?
Participants attend a screening assessment. They then are randomly allocated to one of two groups. Those in the control group receive no treatment. Those in the second group receive 32 weeks of treatment with exenatide QW and dapagliflozin. Those in the third group receive dapagliflozin. Participant's attend the clinic visits to assess their body weight, have blood taken, and measure their physical activity. Participants also attend test meal visits where they have a test meal and are assessed after. The outcomes of the different groups on participants body weigh, food intake, metabolic measures and cardiovascular function are assessed.

What are the possible benefits and risks of participating?
It is hoped that the treatments will help. However, this cannot be guaranteed. The information gained from this study may help to improve the future treatment of patients with T2DM. By taking part in the study participants will gain knowledge regarding general wellbeing including; blood pressure, weight, heart and arterial function and body composition. Possible disadvantages and risks of taking part
Include inconvenience of the time taken for the visits to the research centres, the risks involved in blood sampling are very small. Occasionally there is bruising due to leakage from a blood vessel but this is rare with good practice. All blood results will be reviewed carefully to avoid

missing any abnormality. If any significant abnormality is found, we will send the report to your GP who will be able to take it further. There are no known risks with ultrasound scanning. DEXA (dual-energy X-ray absorptiometry) uses very low doses of x-ray. Everyone is exposed to radiation from natural sources all the time. DEXA is very similar to the background radiation we are exposed to every day. Some people may find the scanner claustrophobic, or uncomfortable and participants will be supported by the research team. There are no known risks in properly conducted MRI scanning. Certain precautions need to be observed as it involves a strong magnet. Most importantly, an MRI cannot be performed on participants fitted with a heart pacemaker, mini-defibrillator or neurostimulator or have an artificial heart valve; surgical clips in the head; or for any injury which may have left metal particles in the eye, head, or elsewhere in the body. Occasionally research studies using MRI scans or echocardiograms reveal unexpected abnormalities, which require medical follow-up, either for further investigation or (more rarely) treatment. The scans we do are for research purposes, but they are reviewed carefully to avoid missing any abnormality. If any significant abnormality is found, the participants GP will be notified and the GP will be able to take it further.

Where is the study run from?
1. University Hospital Aintree (UK)
2. University of Liverpool (UK)
3. Liverpool Magnetic Resonance Imaging Centre (UK)

When is the study starting and how long is it expected to run for?
July 2016 to March 2022 (updated 02/02/2021, previously: January 2019)

Who is funding the study?
AstraZeneca (UK)

Who is the main contact?
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Public

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Additional identifiers

EudraCT/CTIS number
2015-005242-60

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
36378

Study information

Scientific Title
RESILIENT: RandomisEd, controlled, double blind Study to assess mechanistic effects of combination therapy of dapagliflozin with Exenatide QW versus dapagliflozin alone in obese (BMI>30 kg/m2) patients with Type 2 diabetes mellitus

Acronym
RESILIENT - Version 3.0

Study objectives

The primary objective of the study is to compare the adjusted mean reduction in total body fat mass from baseline following 32 weeks of treatment with exenatide QW and dapagliflozin versus dapagliflozin alone compared with control

Ethics approval required
Old ethics approval format

Ethics approval(s)
North West - Liverpool Central Research Ethics Committee, 17/08/2016, ref: 16/NW/0496

Study design
Randomized; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
See study outputs table

Health condition(s) or problem(s) studied
Specialty: Diabetes, Primary sub-specialty: Type 2; UKCRC code/ Disease: Metabolic and Endocrine/ Diabetes mellitus

Interventions
The primary objective of the study is to compare the adjusted mean reduction in total body fat mass from baseline following 32 weeks of treatment with exenatide QW and dapagliflozin versus dapagliflozin alone compared with control (placebo). There are no follow-up procedures.

Participants are asked to attend Clinical Sciences, Aintree University Hospital for a screening visit. This may take place up to 42 days but no less than 2 days before randomisation. An informed consent form must be signed before any study-specific procedures are undertaken. Randomised participants are then be asked to attend on further visits to receive the exenatide QS/sham injection and to collect a weekly prescription of dapagliflozin/placebo as well as a maximum of 15 additional study visits dependent on consent. These additional visits are as follows;

Screening Assessment (~1 hour) at Clinical Sciences, Aintree University Hospital:
This is an initial Screening Visit to determine eligibility to take part in the trial which lasts for 32 weeks. Participants are guided through a set of questions by a member of our research team. If they are not eligible to take part then the reasons are explained in as much detail as possible.

Clinical Sciences at University Hospital Aintree:
Baseline Visit and Trial treatment weeks 2, 4, 8, 12, 16, 20, 24, 28 & 32.
Participants attend these visits having fasted, nothing to eat or drink (except tap water) since the night before.

Anthropometrics - (~10min) (Baseline visit and Trial Treatment weeks 4, 16 and 32 at Eleanor Rathbone, University of Liverpool):
Body weight and height, waist and hip circumference, blood pressure and fat and fat-free mass using a bio-impedance analyser are recorded.

Biochemical Tests - (~5min): All participants have a routine 10 ml blood sample taken for HbA1c, fasting plasma glucose, renal profile (to include electrolytes, urea & creatinine and eGFR), insulin, lipid profile and liver function tests (LFTs to include ALT, AST and bilirubin), insulin, non-esterified-fatty acids (NEFA), 3-hydroxybutyrate. Insulin sensitivity is measured by HOMA-IR. Fasting plasma glucose (FPG) and estimated glomerular filtration rate (eGFR) are measured every 2-4 weeks. This allows researchers to determine the amount of filtered glucose calculated from the product of the FPG (mg/dl) and eGFR (ml/min/1.73 m2)(2).

Physical Activity Monitoring/Food Diary - Participants are issued with a multi-sensor array armband to assess the dimensions of activity (frequency, intensity, duration and type of activity) and associated Physical Activity Energy Expenditure (PAEE) and Total Energy Expenditure (TEE). This is to be worn for 4-days prior to the first study visit, excluding bathing/showering and prior to each test meal. Patients will be asked to complete a food diary detailing exactly what they eat and drink over the same 4-day period.

Test meal visits - (~9 hours) Clinical Sciences, University Hospital Aintree:
(Baseline visit and Trial Treatment weeks 4, 16 and 32)
This includes the following:
Assessment of food intake and subjective appetite sensations using test meals (PROBE days):
Pre-study instructions: On the day preceding each study visit, participants will be asked to keep their food intake, fluid intake and activity levels similar and not to consume any alcohol or take part in vigorous exercise. On each pre-study evening, participants are requested to keep a diary record of the food and drink consumed and the activities undertaken from 5.00 pm until they retired for the night. They are asked not to eat or drink anything except water from 12 midnight until they attend the laboratory at the study centre the following morning at 8am. Participants are advised to bring any of their documented medications with them on the morning of the study day to take prior to their breakfast meal. Participants are weighed and their pulse and blood pressure recorded. An explanation and demonstration of visual analogue scale questionnaires, appetite questionnaires and the ventilated hood are given.
Calculation of energy density of fixed energy breakfast Resting metabolic rate (RMR) is measured on the morning of the procedure prior to the fixed energy breakfast using an indirect calorimeter (GEM) fitted with a ventilated hood. Participants remain awake but motionless in a supine position for 45 minutes with RMR calculated from respiratory data averaged over the final 30 minutes of assessment.

Fixed-load breakfast:
At 9am participants are seated in individual cubicles and administered a fixed load breakfast (cereal with milk, toast and preserve and orange juice) relative to resting metabolic rate (~25% energy needs) as determined by the indirect calorimetry. In addition to the fixed-load breakfast items, at the first visit, participants are offered water or a hot drink of tea or coffee with additional semi-skimmed milk (35 g) and sugar or sweetener if desired. If requested, this drink has to be consumed on each subsequent visit. Participants are asked to consume everything

presented within twenty minutes and are instructed not to eat or drink anything except that provided by the researcher
1. Ad libitum lunch to assess energy intake and food choice An ad libitum lunch are served four hours post breakfast. Participants are presented with more food than they are likely to consume and instructed to eat as much as they like until they feel comfortably full, from the choice of foods and water offered, taking as long as they wished, and to signal when they have finished. The ad libitum test lunch consists of a multiple item buffet at lunch (mix of high and low fat and sweet and savoury items). A change in food choice (to high fat items) could explain increased caloric intake without a change in amount (g) of food. Water (500 ml) are also provided.
2. Assessment of subjective appetite sensations. Throughout the testing period, before and after meals and at hourly intervals, participants are asked to complete visual analogue scales (VAS) to record their subjective ratings of appetite on a 100 mm line between anchor phrases of 'not at all' or 'extremely' in response to specific questions. VAS is used to measure:
Hunger; Fullness; Satisfaction; Prospective Food Consumption; Desire to Eat; Thirst; Nausea
3. Psychology of Appetite Questionnaires. A battery of questions are taken along with body weight at baseline and weeks 4, 16 and 32, pre and post treatment to assess drug effects on experience of appetite, cravings, feeling of control and the power of the food and food environment over eating behaviour and ability to resist consuming energy dense palatable food. Participants are asked to complete a series of questionnaires.
4. Indirect Calorimetry. Energy expenditure and respiratory quotients (RQ) are measured on the morning of the test meal visit prior to the fixed energy breakfast using an indirect calorimeter (GEM) fitted with a ventilated hood and derived using the modified Weir equation. Participants remain awake but motionless in a supine position for 45 minutes with RMR calculated from respiratory data averaged over the final 30 minutes of assessment. The first 15 minutes of each measurement are discarded to allow for complete acclimatisation to the hood and the recumbent position.
5. 24 hour urinary glucose excretion: A container is provided at the screening assessment to bring to the next visit. Analysis of the 24-hour urine collections include the following:
5.1. Urinary nitrogen (UNit) and urinary sucrose (USuc) concentration to determine dietary protein and sucrose intake respectively
5.2. Urinary sodium concentration (UNa) to determine urinary sodium excretion
5.3. Urinary glucose concentration (UGluc) to measure urinary glucose excretion

Imaging Visits: University of Liverpool MARIARC and/or Eleanor Rathbone (Baseline and week 32)
Body Composition
Participants undergo MR scanning in a 3.0T Siemens scanner at the University of Liverpool Magnetic Resonance and Image Analysis Research Centre (MARIARC) and DEXA (dual-energy X-ray absorptiometry) scanning situated in the Eleanor Rathbone Building, Department of Psychological Sciences, University of Liverpool. The following parameters are evaluated:
1. Assessment of whole body, subcutaneous, visceral and liver fat (60 mins) Whole body Magnetic Resonance Imaging (MRI) will be undertaken and whole body and abdominal subcutaneous and visceral fat content determined using serial transverse sections. In the same scanning session triglyceride deposition (steatosis) in the liver, pancreas and skeletal muscle (tibialis anterior) will be measured using proton magnetic resonance spectroscopy (1H-MRS).
2. Assessment of lean body mass (15 mins) Total fat free/lean body mass are determined using DEXA (dual-energy X-ray absorptiometry).

Intervention Type
Drug

Phase

Phase III/IV

Drug/device/biological/vaccine name(s)
Dapagliflozin 10 mg od and matching Placebo, Exenatide 2 mg and placebo (Saline fluid)

Primary outcome measure
Primary outcome is measure by adjusted mean change in total body fat mass from baseline to week 32 quantified by DEXA.

Secondary outcome measures
1. Metabolic measures are measured using HbA1c (the principal measure of glycaemic control), 24 hour urinary glucose excretion and hepatic glucose output, measured using hyperinsulinaemic, euglycaemic clamp and stable isotope infusions of 2H-glucose
2. Measures of food intake, feeding behaviour and appetite using test meal study days
3. Changes in body weight and fat volume and distribution using MRI/MRS using visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT) and Liver fat
4. Changes in cardiovascular function using indices of myocardial systolic and diastolic function using transthoracic echocardiography (Tissue Doppler Imaging) and endothelial function: Flow mediated dilatation will be measured in response to an ischaemic stimulus using brachial ultrasound

Overall study start date
04/07/2016

Completion date
31/03/2022

Eligibility

Key inclusion criteria
1. Males or females, age 18-65 years
2. A clinical diagnosis of type 2 diabetes
3. Glycosylated haemoglobin (HbA1c) ≥6.5% but ≤11% (48-97mmol/mol)
4. Currently treated with either diet or any combination of metformin, DPPIV inhibitors* and sulphonylureas (excluding patients treated with pioglitazone or insulin). *DPP-IV inhibitors will require wash out period of four weeks
5. BMI 30-50 kg/m2
6. Patients who are receiving the following medications must be on stable treatment regimen for a minimum of 2 months prior to screening:
7. Thyroid hormone replacement
8. Antidepressants

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
65 Years

Sex
Both

Target number of participants
Planned Sample Size: 120; UK Sample Size: 120

Key exclusion criteria
1. Type 1 diabetes mellitus
2. History of diabetic ketoacidosis or hyperosmolar non-ketotic coma
3. Renal impairment: eGFR less than 60 ml/minute/1.73m2
4. Hyperthyroidism
5. Hypothyroidism (subjects with a normal TSH and free T4, and on a stable dose of thyroxine for at least 3 months may
be included)
6. Uncontrolled hypertension (SBP >160mmHg/DBP >110mmHg)
7. Congestive heart failure class III-IV
8. Recent (< 6 months) myocardial infarction
9. Severe hepatic impairment
10. Significant cardiac dysrhythmias (including pacemaker or ICD)
11. Previous stroke
12. Hypovolaemia
13. Previous history of acute pancreatitis
14. History of medullary thyroid cancer or bladder cancer
15. Presence of any other medical condition that would, in the opinion of the investigator or their clinician, preclude safe
participation in the study. This decision should be informed by dapagliflozin and exenatide precautions for use
statements which will be provided to all clinicians and the research team
16. Alcohol consumption in excess of daily recommended limits (21 units/week females, 28 units /week males)
17. Any history of internal metal, pacemakers, ferromagnetic metallic implants, intraocular foreign bodies or cerebral
aneurysm clips (exclusion from MR scanning)
18. History of seizures or unexplained syncope
19. ALT > 3 x ULN
20. AST > 3 x ULN
21. Bilirubin > 2 x ULN
22. Haemoglobin ≤ 10.5 g/dL (≤ 105 g/L) for men; haemoglobin ≤ 9.5 g/dL (≤ 95 g/L) for women
23. eGFR <60 ml/minute/1.73m2
24. Unexplained haematuria
25. Weight < 60kg and >150kg (due to MRI limitations)
26. BMI <30 kg/m2 and >50 kg/m2
27. Recent major change in body weight (> 3kg loss or gain in preceding month)
Subjects with a history of any serious hypersensitivity reaction to GLP1-RA or SGLT2 inhibitor
28. Participant should have no allergies against metacresol (the preservative in insulin vial)
29. History of anaphylaxis to food
30. Known food allergies or food intolerance
31. Known hypersensitivity to heparin

32. Known hypersensitivity to IV catheter equipment
33. Females of childbearing age who are not using adequate contraceptive methods or who are planning a pregnancy in
the next 6 months
34. Women who are pregnant or breastfeeding
35. Diabetes treated with pioglitazone, SGLT2 inhibitors, GLP-1 analogues or insulin,
36. Use of other weight loss medication or any drug that might affect body weight or appetite (including antipsychotics,
orlistat or corticosteroids)
37. Patients who are currently receiving a loop diuretic that cannot be discontinued
38. Active or previous substance abuse or dependence
39. Prisoners or subjects who are involuntarily incarcerated
40. Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g. infectious disease)
illness

Date of first enrolment
25/10/2017

Date of final enrolment
31/07/2021

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
University Hospital Aintree
Aintree University Hospital NHS Foundation Trust
Clinical Sciences Centre
Longmoor Lane
Liverpool
United Kingdom
L9 7AL

Study participating centre
University of Liverpool
School of Psychology
Eleanor Rathbone Building, Bedford Street South
Liverpool
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L69 7ZA

Study participating centre
Liverpool Magnetic Resonance Imaging Centre
LiMRC (formerly MARIARC)
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Sponsor information

Organisation
University of Liverpool

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Sponsor type
University/education

ROR
https://ror.org/04xs57h96

Funder(s)

Funder type
Government

Funder Name
AstraZeneca

Alternative Name(s)
AstraZeneca PLC, Pearl Therapeutics

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
It is anticipated that the data from the study will be published in at least four separate manuscripts consistent with the numerous secondary outcome measures of the following sub-divisions of data:

Study protocol: The study protocol will be published in its own right after ethical approval. We will target journals such as BMJ Open.

Metabolic and body composition changes: Co-administration of an SGLT2 with a GLP1 receptor agonist (GLP1-RA) and change in HBA1c and weight (kg) from baseline is highly anticipated. We will aim for publication of the derived data in high impact, peer-reviewed journals such as Diabetes Care and Diabetologia.

Metabolic and body composition changes including the visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT) and liver and pancreatic fat measurements (MRI/MRS) and changes in hepatic glucose output will be published in metabolic journals such as The Journal of Clinical Endocrinology and Metabolism.

Energy balance changes: including food intake (g and kcal), food choice (macronutrients) and subjective experience of appetite will be derived from measurements during test meals. We will target journals of obesity and the psychology of appetite to include the International Journal of Obesity and Appetite.

Changes in cardiovascular function: including measures of myocardial systolic and diastolic function using transthoracic echocardiography (Tissue Doppler Imaging) and of endothelial function measured in response to an ischaemic stimulus using brachial ultrasound. We will target diabetes journals such as Diabetes Care and Diabetologia but if unsuccessful will send to a cardiology journal.

Implementation of findings: To date there is no evidence around the co-administration of GLP-RA with SGLT2s despite good rationale to do so. Implementation of findings may lead to change of clinical practice guidelines after consultation.

Public dissemination: A clear ‘plain English’ summary of the findings will be created so that they are widely accessible to participants and the wider patient group. Attendance at diabetes awareness days at the hospital and in the community will also facilitate transfer of knowledge.

Intention to publish date

30/09/2022

Individual participant data (IPD) sharing plan

The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication

IPD sharing plan summary

Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version V3	12/03/2017	25/01/2018	No	Yes
HRA research summary			28/06/2023	No	No
Protocol article		20/07/2021	14/02/2024	Yes	No