(To be printed on Hospital Trust headed paper)

Participant Information Sheet

Please read carefully if you think you would like to take part in our study:

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/m^2) patients with Type 2 diabetes mellitus.

We would like to invite you to take part in our research study. Before you decide we would like to explain why the research is being done and what it would involve for you.

Please take the time to read this information sheet carefully and be sure to ask any questions you have, and if you wish, discuss it with friends, relatives or your GP. You do not have to make an immediate decision with regards to whether you wish to take part in the study.

- **Part One** tells you the purpose of the study and what it would involve if you take part.
- **Part Two** gives you more detailed information about the conduct of the study.
- **Part Three** tells you about optional studies you may be asked to participate in.

PART ONE

Why have I been chosen?

We are inviting patients with Type 2 diabetes (T2DM) to take part in this research project. You are being asked to take part because your doctor (from the diabetes clinic) has identified you as a potentially suitable candidate for the study.

Participation will be subject to a short screening questionnaire to ensure that you match the eligibility criteria for the study.

What is the purpose of the study?

The purpose of this study is to determine the benefits of using dapagliflozin (an SGLT2 inhibitor) and exenatide QW (once a week GLP-1 receptor agonist) in combination.
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.

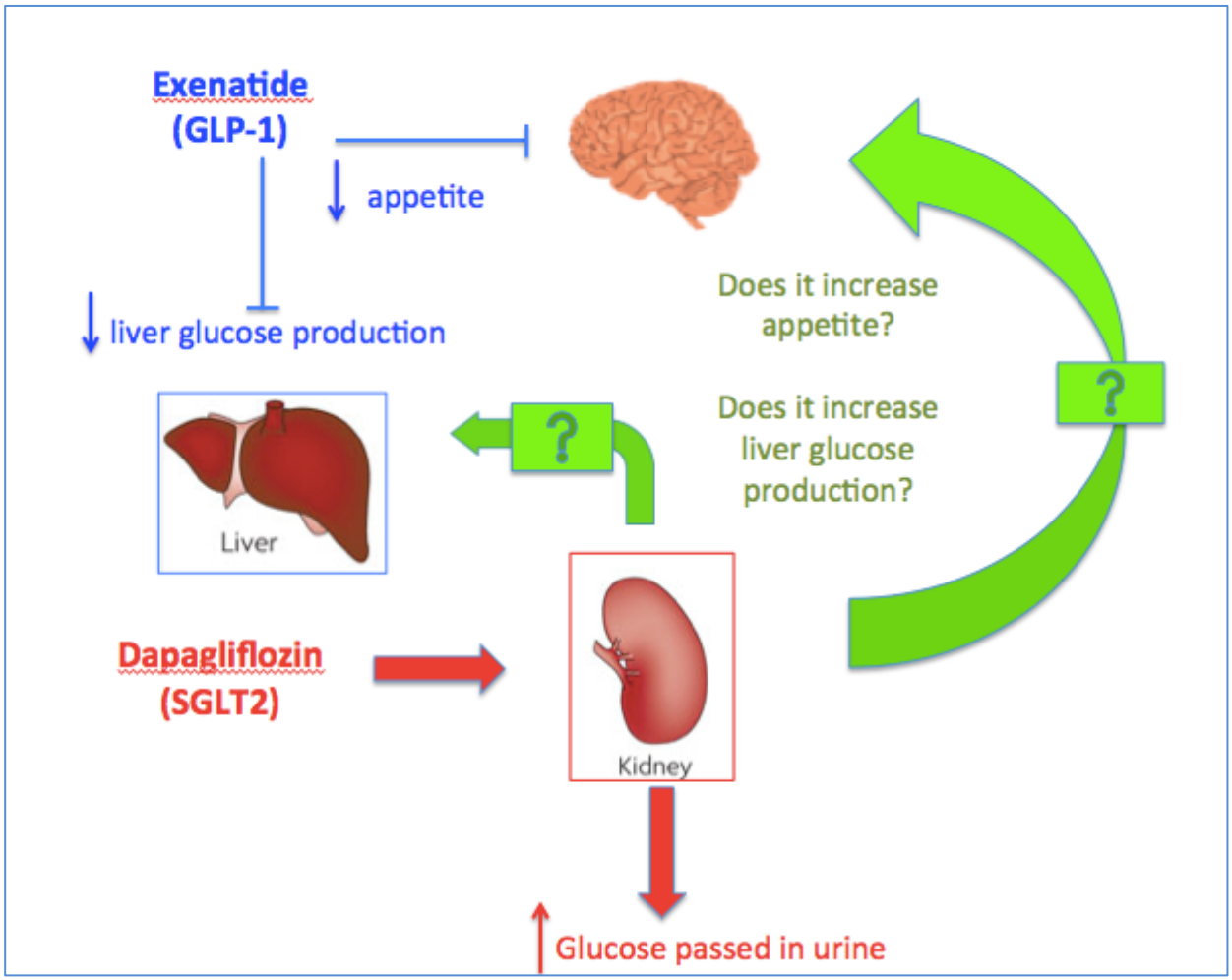

Figure 1: How SGLT2 inhibitors and GLP-1 receptor agonists work.

Do I have to take part?
No - It is up to you – you do not have to take part.
One of our team will go through the information sheet with you. If you do decide to take part you will be asked to sign a consent form but you are free to withdraw at any time and without

giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will it involve if I take part?
Your diabetes will continue to be controlled medically throughout the course of the study. Both of the drugs that we are studying are routinely used in the diabetes clinic. If you require any further clarification/explanation then please ask a member of the research team or seek advice from your diabetes consultant who will be aware of this study.

If you decide to take part, following the Screening visit, you will be asked to attend Clinical Sciences, Aintree University Hospital to receive the weekly exenatide QW/sham injection and to collect your prescription of dapagliflozin/placebo as well as a maximum of 12 study visits over a 32 week treatment period as follows;

SCREENING ASSESSMENT *(~1 hour)*
Clinical Sciences, Aintree University Hospital

This is an initial Screening Visit to determine if you are eligible to take part in the trial which will last for 32 weeks. You will be guided through a set of questions by a member of our research team. If you are not eligible to take part then the reasons will be explained to you in as much detail as possible.

Your clinical details will be collected during a brief interview or where possible from your clinic notes. We will examine your chest and abdomen and record your height, weight, waist and hip circumference, heart rate and blood pressure. An ECG will be performed. We will ask if you could do a urine sample. A routine 10 ml blood sample for full blood count, renal profile, glucose, HbA1c, liver function and thyroid function will be taken.

In this type of study we do not know which way of treating patients is best. To find out, we need to make comparisons between the different treatments. We put people into groups and give each group a different treatment; the results are compared to see if one treatment is better than another. To try to make sure the groups are the same to start with, each patient is put into a group by chance (randomly). The results are then compared.

So, if you agree to take part and you meet the criteria to participate, you will be allocated to one of three groups at random (See Figure 2):

Arm A. Control – placebo tablet and sham injection
Arm B. Dapagliflozin and placebo (sham injection)
Arm C. Dapagliflozin and exenatide QW injection

Each arm of the study will have equal numbers of patients allocated to it by a process of chance known as randomisation. This means that a third of the patients will be in each arm. Allocating patients in this way allows the results to be compared more accurately. The respective

treatment interventions are described in more detail later on and will also be fully explained verbally by a member of the research team.

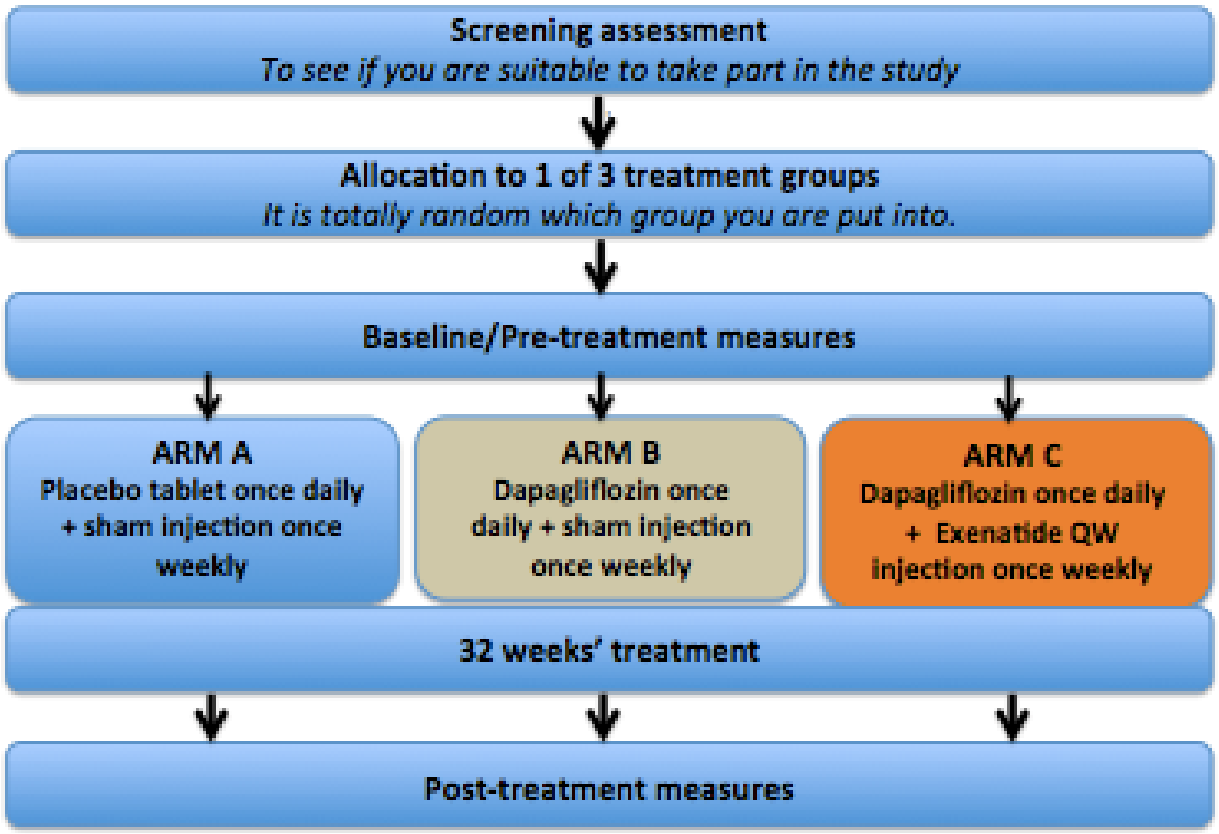

Figure 2: Overview of what the study involves.

The tests we propose are for research purposes and will be performed at the following centres (directions attached):

- Clinical Sciences at Aintree University Hospital
- Eleanor Rathbone Building, University of Liverpool
- MARIARC (Magnetic Resonance and Image Analysis Research Centre, University of Liverpool)

Activity Monitor and food diary: A member of the research team will issue you with an armband which is to be worn for 4-days (excluding bathing/showering) prior to your first study visit and prior to each test meal. You will be asked to complete a food diary detailing exactly what you eat and drink over the same 4-day period (see example on the next page). The monitor and food diary will provide the research team with useful information regarding your 'normal' daily activities and lifestyle habits. **Please bring this with you to your next scheduled visit.**

DAY: MONDAY DATE: 1ST AUG 2016

TIME OF DAY	NAME OF FOOD EATEN OR DRINK INGESTED	SIZE OF PORTION (i.e. large or small bowl, large cup, 2 slices, 200 ml etc)
08:00	ORANGE JUICE	SMALL GLASS
08:00	TOAST + JAM	2 SLICES
12:30	CHEESE SALAD SANDWICH	2 SLICES
12:30	TEA + MILK	CUP
15:00	1 MUFFIN	NORMAL
15:00	TEA + MILK	CUP
18:00	CHICKEN, CHIPS	LARGE PLATE
	AND PEAS	

Figure 3: Example how to complete the Food Diary.

Blood Glucose Monitoring: A blood glucose monitoring machine will be given to you and instructions given on how to use it. We will ask you to check your blood sugar a minimum of once a day with additional checks if you have symptoms of low blood sugar (hypoglycaemia), are unwell or if required for certain tasks e.g. driving. You will be provided with a patient diary to record your blood glucose results each day.

Visit 1 – Appetite Assessment (~9 hours)
Clinical Sciences, Aintree University Hospital

You will be asked to attend the Clinical Sciences Centre, University Hospital Aintree at ~8am in the morning. This can be easily accessed by public transport (bus and rail) and there is a directions sheet provided by the research team for your convenience. You should not eat or drink anything but water from 12 midnight the night before. You will also be advised to avoid any alcohol or vigorous exercise. You may take any medications you would usually take.

- ***Anthropometric data*** (~10min)*:* A member of the research team will guide you through an anthropometric assessment. This will involve measuring your weight, hip and waist circumference, and weighing you on a set of bio-impedance scales which provide an estimate of body composition. Your heart rate and blood pressure will be recorded.

- ***A fasting blood sample*** (~5min)**:** A routine blood sample (10mls which is approximately 2 teaspoons) will be taken from a vein in your arm for various biochemical tests including routine tests for patients with diabetes, and some that are special tests used in this study.

- ***24 hour urinary glucose excretion:*** A container will be given to you at the beginning of the appetite assessment day to begin collection.

- ***Calculation of resting metabolic rate*** *(~45 mins):* Before your first breakfast we will work out your resting metabolic rate (RMR). The resting metabolic rate determines the amount of energy (calories) your body is using at rest. This measurement is made by analyzing the amount of oxygen your body uses and the amount of carbon dioxide your body produces. During the test you will be asked to lie down on a bed for 45 minutes. You will fitted with a ventilated hood that sits over your head (looks a bit like an astronaut's helmet). The hood will not provide you with extra air, you will only be breathing from the air in the environment.

- ***Fixed-load breakfast*** *(~20 mins):* We will ask about your dietary requirements during the screening visit. You will be given a standard breakfast meal (cereal with milk, toast and preserve and orange juice) on each study visit. The amount you are given will be adjusted for your resting metabolic rate. You will have access to water. Should you want a hot drink of tea or coffee (with additional milk or sugar/sweetener) we ask that you drink this at each subsequent visit.

- ***Ad-libitum lunch:*** *A buffet style lunch* will be served four hours after your breakfast. You can eat what you like but we will ask you to tell us when you are finished. You will have access to water.

- ***Assessment of appetite:*** Throughout the testing period, before and after meals and at hourly intervals participants will be asked to complete ratings of appetite e.g. hunger, fullness. An example of one of these questions and how to fill it in is given below (See Figure 3).

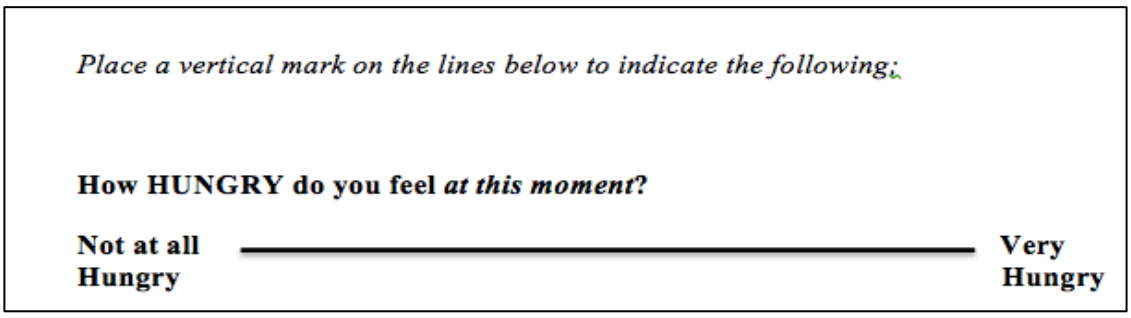

Figure 4: Assessment of appetite using a visual analogue score (VAS)

- **Appetite questionnaires:** Whilst you are visiting the centre for assessment of your appetite we will give you a series of questionnaires to complete. There are 6 questionnaires in total which will take approximately 30 minutes in total to complete.

You can complete these on your own or one of the research team can go through the questions with you.

Anthropometry (weeks 0, 2, 4, 8, 12, 16, 20, 24, 28 and 32)
Body weight and height, waist and hip circumference and body composition will be repeated on several occasions during the study.

Fasting Blood Sample (weeks 0, 2, 4, 8, 12, 16, 20, 24, 28 and 32)
A fasting blood sample will be repeated at intervals during the study.

24–hour Urine Collections (weeks 0, 4, 16 and 32)

Assessment of Body Composition (Weeks 0 and 32)
Body composition measurements including MRI AND DEXA. (*Participants who consent to take part in the optional doubly labelled water procedure will have an additional DEXA at weeks 4 and 16).*

Appetite Assessment (Weeks 0, 4, 16 and 32):
Assessment of appetite including test meals and questionnaires will be repeated before, during and at the end of treatment.

Visit 2a and 2b - Imaging Visits – Assessment of Body Composition
MARIARC and Eleanor Rathbone Building, University of Liverpool

The researcher will meet you at around 9am at the MARIARC Centre on Pembroke Place which is a few hundred yards from the Royal Liverpool University Hospital and Dental Hospital. This can be easily accessed by public transport (bus and rail) and there is a directions sheet provided by the research team for your convenience. What to expect during the study day is detailed below.

2a - Assessment of whole body composition - Magnetic Resonance Imaging (MRI) *(~60 mins)*
We will measure your whole body composition and fat content using a scan known as Magnetic Resonance Imaging (MRI). You will be asked to fill in a short safety screening form to make sure there are no reasons why you would not be suitable for magnetic resonance scanning. If you suffer from claustrophobia then it's possible that you may find the scan distressing. The radiographer and a member of the research team who will be accompanying you will talk you through options to lessen any potential distress. You will also be given a hand held buzzer during every scan which if pressed will stop the scan immediately and you will be aided out of the scanner. You will be asked to wear a gown (changing rooms are provided) and remove items which are affected by the magnetic field (e.g. hearing aids, mobile phones, keys, coins, pens, credit cards (secure lockers are provided). While inside the scanner, you will be asked to lie as still as possible.

2b - Assessment of fat free tissue **- DEXA (dual-energy X-ray absorptiometry)** ***(****~15mins)* DEXA (dual-energy X-ray absorptiometry) uses low doses of x-ray to measure your bodies composition (e.g. amount of fat and muscle tissue). Please see separate patient information sheet for more information (Participant Information Sheet. Additional Details: Measurement of Body Composition using DEXA). This is likely to take place on the same day as visit 2a (but may be on a different day) at the Eleanor Rathbone Building.

What treatment will I receive?

Arm A - Control group (no intervention)
You will be asked to continue with your usual anti-diabetes medications as advised by your consultant. You will be given a placebo tablet once a day. You will be provided with a patient diary to record when you take each tablet. A placebo injection containing sterile water will be administered as a once-weekly subcutaneous injection in the abdomen, thigh or upper arm.

Arm B – Dapagliflozin and placebo (sham injection)
You will be given 10mg dapagliflozin 10mg to be taken once daily. You will be provided with a patient diary to record when you take each tablet. A placebo injection containing sterile water will be administered as a once-weekly subcutaneous injection in the abdomen, thigh or upper arm. Therapy will be initiated under the supervision of a diabetes nurse specialist, research nurse or clinician who will continue to give you the injection on a weekly basis. You will be asked to continue with your usual anti-diabetes medications as advised by your consultant.

Arm C – Dapagliflozin and exenatide QW
You will be given 10mg dapagliflozin to be taken once daily. You will be provided with a patient diary to record when you take each tablet. Exenatide QW will be prescribed and administered as a once-weekly subcutaneous injection in the abdomen, thigh or upper arm. Therapy will be initiated under the supervision of a diabetes nurse specialist, research nurse or clinician who will continue to give you the injection on a weekly basis. You will be asked to continue with your usual anti-diabetes medications as advised by your consultant.

What are the side effects of the treatment I may receive when taking part?
Study staff will look out for any side effects and offer treatment should they occur.

Dapagliflozin: The most common side effects (may affect 1 in 10 people) reported with dapagliflozin include infections such as urinary tract infections or cystitis and passing more urine which may lead to mild dehydration and dizziness. Drinking plenty of fluids helps to reduce the risk of these side-effects. If you do suffer any of the known side-effects or any other symptoms during the study you should report them to the study team.

Dapagliflozin is considered to be a safe drug but there are few rarer side effects that it is important we tell you about in detail:

- In rare cases (may affect 1 in a 1000), patients with type 2 diabetes can develop diabetic ketoacidosis (DKA), a serious condition that may require hospitalisation. Symptoms of DKA could include, but are not limited to, feeling sick or being sick, vomiting, abdominal pain, rapid weight loss, thirst, feeling tired, shortness of breath and high blood sugar. DKA with normal or near normal blood sugar has been reported in patients treated with an SGLT2 inhibitor (such as dapagliflozin). You will be monitored closely for the development of DKA and you are advised to **contact your study doctor, or seek medical attention immediately**, if you experience any of the symptoms listed above.

- Acute kidney injury is a sudden damage to the kidneys that causes them not to work properly. Cases of acute kidney injury, some requiring hospitalisation and dialysis, have been reported in patients receiving SGLT2 inhibitors (such as dapagliflozin). About half of the cases occurred within 1 month of starting the the medication and most patients improved after stopping the drug.

  Please seek medical attention immediately if you experience signs and symptoms while taking these medicines such as:
  - Decreased urine amounts
  - Swelling in your legs or feet

  Please talk with the study team immediately if you are:
  - Eating or drinking less due to illness or fasting
  - Losing fluids due to vomiting, diarrhoea, or excessive heat exposure

  The study team may decide it is appropriate to temporarily stop taking study medication in these situations. Do not stop taking any of your medication without first talking to member of the research team or a healthcare professional.

- Patients with diabetes (especially those with poorly controlled diabetes and pre-existing problems with the heart and blood vessels) are at increased risk of infection and ulceration which can result in lower limb amputations. As a result your feet will be assessed at the beginning of the study and you will be reminded about how to look after your feet at each visit.

Exenatide QW: The most common side effects (may affect 1 in 10 people) reported with exenatide QW include low blood sugars (*hypoglycaemia*), mild to moderate nausea and diarrhoea. Much less common side effects include headache, vomiting, constipation, abdominal pain and dyspepsia (may affect less than 1 in 100 people). These reactions usually diminish within a few days or weeks on continued treatment.

Cases of inflammation of the pancreas (pancreatitis) have been reported with patients receiving GLP-1 RA (such as exenatide QW). Only a few cases have been reported. If you experience persistent or severe stomach pain with or without vomiting we would advise you to contact your **study doctor, or seek medical attention immediately**.

What are the alternatives for treatment? If you decide not to participate in this study, or are not suitable for the study, then your doctor will discuss other treatment options with you.

What are the possible benefits of taking part?
We hope that the treatments will help you. However, this cannot be guaranteed. The information we get from this study may help us to improve the future treatment of patients with T2DM. By taking part in the study you will gain knowledge regarding your general wellbeing including; blood pressure, weight and body composition.

What are the possible disadvantages and risks of taking part?

- There will be the 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.

- DEXA (dual-energy X-ray absorptiometry) uses very low doses of x-ray. We are exposed to radiation from natural sources all the time. A DEXA gives is very similar to the background radiation we are exposed to every day.

- Some people may find the scanner claustrophobic, or uncomfortable and we will check this with you. There are no known risks in properly conducted MRI scanning. Certain precautions need to be observed as it involves a strong magnet. ***Most importantly, you cannot have an MRI if you are fitted with a heart pacemaker, mini-defibrillator or neurostimulator or have an artificial heart valve; if you have surgical clips in your head; if you have ever had an injury which may have left metal particles in your eye, head, or elsewhere in your body.***

- Occasionally research studies using MRI scans 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, we will send the report to your GP who will be able to take it further.

What expenses will I receive?

You will not be paid for taking part in this study however you will receive reimbursement for any reasonable travel costs associated with attending study visits and will receive compensation to cover the time taken for attending certain visits (see below). For study visits where you have to attend fasted, a breakfast meal will be provided before leaving clinic. The following compensation payments are available in acknowledgement of any inconvenience (maximum payable £500):

- £25 Imaging visits (visits 1, 3, 6, 11)
- £50 Test meal days (visits 1, 3, 6, 11)
- £50 Optional Insulin Clamp (visits 1, 11)
- £50 Optional Brain Imaging and Appetite Assessment (Visits 1, 10)

If you are in receipt of any benefits you should check whether these will be affected by the compensation.

What happens when the research study stops?

After you have finished the study your study doctor will decide on the best treatment for your diabetes. It is important to note that whilst both treatments are used regularly in the diabetes clinics we cannot guarantee it will be suitable to continue the treatment used in the study.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information is given in Part 3 of this information sheet.

Will my taking part in this study be kept confidential?

Yes. All the confidential information about your participation in this study will be kept confidential. The detailed information on this is given in Part 3.

Contact for Further Information

Should you have any further queries regarding this study or about any of the treatments described above, **please contact:**

Appropriate job title:

[Trust to insert contact details]

Contact Number is:

[Trust to insert contact details]

This completes Part One of the Information Sheet. If the information in Part One has interested you and you are considering participation, please continue to read the additional information in Part Two before making any decision.

PART TWO

What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment/drug that is being studied. If this happens, your doctor will tell you about it and discuss with you whether you want to or should continue in the study. If you decide to withdraw your doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

On receiving new information your doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue.

If the study is stopped for any other reason you will be told why and your continuing care will be arranged.

What will happen if I don't want to carry on with the study?

You are free to withdraw at any time throughout the course of the project, without explanation. Results up to the period of withdrawal may be used, if you are happy for this to be done. Otherwise you may request that they are destroyed and no further use is made of them.

What if there is a problem?

If you have concerns about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions. If you remain unhappy and wish to complain formally the normal National Health Service complaints mechanisms will still be available to you (Details can be obtained from the PALS team, University Hospital Aintree, phone: 0151 5293287)

In the unlikely event that you become ill or suffer any injury as a direct result of a procedure of the study, the study doctor will arrange for the correct treatment. In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action, but you may have to pay your legal costs.

What happens to the information collected about me?

If you join the study, some parts of your medical records and the data collected for the study will be looked at by authorised persons from Liverpool Clinical Trials Unit or their collaborators who are also involved in organising this research project. These individuals are health care professionals who are experienced in clinical trials. A copy of your completed consent form will be sent to the Liverpool Clinical Trial Unit to allow them to check you have

agreed to the trial. This will be kept in a secure location away from all the study data. Also, the data on the safety of the trial will be reviewed by appropriate oversight committees but no one will be able to identify you. Data may also be looked at by representatives of regulatory authorities and by authorised people from the Trust and other NHS bodies to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant.

Involvement of the General Practitioner/Family Doctor (GP)

With your consent, your GP will be informed of your involvement in the trial. Any other medical practitioners who treat you, e.g. should you be admitted to hospital for any reason, will also be informed.

What will happen to any samples I give?

All of your routine study samples will be analysed at your hospital for the purpose of your treatment. With your permission, we would also like to retain some samples for use in future research studies if informed consent to do so is obtained. The blood and urine samples that you provide will be stored securely in the freezers of the Department of Medicine within the University of Liverpool laboratories.

The researchers at the University of Liverpool work closely with other scientists in the UK, around Europe and outside the European Economic Area. With your permission, your samples may be transferred to these research collaborators for use in future scientific studies. These samples will be used only for investigating T2DM and will not be used for any commercial purposes.

The samples will be kept in a secure place until we need them; nobody outside of the study will have access to **any** confidential information that you give to us. Confidential details (such as your name, address and GP details) will be kept locally and not made available to collaborators.

All samples will be fully anonymised from the point of processing, storage and translational analysis and the researchers carrying out tests on the samples will not be given information they do not need to carry out the tests and analyse the results.

Will any genetic tests be done?

With your permission genetic tests may be performed on blood samples in this study in relation to diabetes. Your personal genetic code is unique to you and if published could be used to identify you. The ability to do this depends on the amount of genetic information published. If we or our collaborators do carry out genetic analysis and if we need to publish some of the genetic sequence, we will ensure that the published sequence is as short as possible and published with minimal details about you (anonymous data). Although the risk of identification is minimal we are specifically asking for your consent for this form of

publication and if you do not wish to allow this analysis we will tag your samples to identify that they should not be used for this type of analysis (see Part Two, Optional Samples).

What will happen to the results of the study?

Upon completion of the study you will be offered a debriefing by a member of the research team to discuss your results, at which time you will be able to ask questions. The overall collective results of the study will be presented and published in medical journals in the future after analysis of the complete data. We will not identify you in any way when the results are presented or published.

They may also be used to apply to the regulatory authorities to make the drug widely available and/or for research related to the development of pharmaceutical products, diagnostics or medical aids. Again you will not be named or identified in any publication.

What rights do I have to the results of the research?

Any information derived directly or indirectly from this research, as well as any patents, diagnostic tests, drugs, or biological products developed directly or indirectly as a result of this research may be used for commercial purposes (e.g. facilitating the future use of the study drugs within this group of patients). You have no right to this property or to any share of the profits that may be earned directly or indirectly as a result of this research. However, in signing this form and donating tissue and/or blood samples for this research, you do not give up any rights that you would otherwise have as a participant in research.

Who is organising and funding the research?

The University of Liverpool is the sponsor of this research and is conducting the research. AstraZeneca are providing funding and drug to the University of Liverpool for this research.

Your doctor will not receive any payment for including you in this study.

None of the health care team will personally receive any payment for running this trial.

Who has reviewed the study?

The study has been reviewed for content by members of the North West Research Ethics Committee – Liverpool Central for ethical considerations.

Thank you for taking the time to read and consider this information sheet. Should you decide to take part in the study, you will be given a copy of the information sheet and a signed consent form to keep.

PART THREE - Optional Study Procedures

1) Additional Blood Samples – Clinical Sciences, Aintree University Hospital

With your agreement we would like to take a further 10ml sample at the same time as your routine bloods at baseline, week 4, week 16 and week 32 to be retained for use in future research studies. These samples are voluntary and you should indicate in box 14 of the consent form if you are happy to have them taken.

Part of this sample may be used for genetic analysis in relation to diabetes. This is also voluntary and you should indicate in box 20 of the consent form if you are happy to take part.

If you do not want to take part in additional blood samples it will not stop you from entering the trial. If you would like any more information please ask your researcher.

2) Cardiovascular Assessment of the Heart – Clinical Sciences, Aintree University Hospital or MARIARC

A small group of patients (20 per treatment arm) will be invited to take part at baseline and week 32.

Blood Pressure Monitoring: A blood pressure monitor will be given to you at the beginning and end of the study to measure your blood pressure over a 24 hour period (excluding bathing and showering). It involves wearing a cuff over your upper arm. You can take this home to wear and bring it with you to your next visit.

Assessment of the size and function of the heart by ultrasound (echocardiography or cardiac echo) (~15 minutes). The echo examination will require you to lie down having an ultrasound probe being placed on your chest whilst images of the heart and blood flow through the heart are recorded.

There are no known risks with ultrasound scanning. Occasionally research studies using echocardiography scans 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, we will send the report to your GP who will be able to take it further.

This part of the study is optional and you should indicate in box 15of the consent form if you are happy to take part. If you do not want to take part in the study procedure it will not stop you from entering the trial.

Assessment of large blood vessel function by ultrasound scanning of the arm and neck

(~40 minutes) Blood pressure measurements from your left arm will be recorded intermittently throughout these scanning procedures. This will comprise of two parts:

- **Arm:** Initially you will be asked to undergo 20 minutes of bed rest, during which time a small blood pressure cuff will be placed below your right elbow. An ultrasound probe will then be placed above the right elbow for 1-minute before the cuff is inflated for 5-minutes. At this point you may feel a loss of feeling, tightness, pins and needles and mild pain in your right arm below the cuff. Immediately after the cuff is deflated images from the ultrasound will be recorded for 3-minutes.

- **Neck:** An ultrasound probe will then be placed on your neck to scan the main artery feeding the brain called the carotid artery. An image of the artery will be obtained to measure the thickness of the wall. This will take approximately 2 minutes.

3) Insulin Clamp - Clinical Sciences, Aintree University Hospital (~8 hours)

A small group of patients (20 per treatment arm) will be invited to take part in a study using a clamp. They are called clamps because your glucose is clamped, or held, at a certain concentration. The clamp is used to measure either how well someone metabolizes glucose or how sensitive an individual is to insulin.

You will be advised to avoid strenuous physical activity and alcohol for 48 hours prior to the assessment. A cannulae will be inserted into a vein in both of your arms so that we can take blood at set intervals and set up a drip (infusion) containing glucose and insulin. The infusion is a stable isotope of glucose and therefore is not radioactive and will not cause long-term harm. We aim to keep your glucose levels at a steady state by measuring and adjusting the infusions every 5 minutes. It is possible that we cause you to have hypoglycaemia (low blood sugar) but this is unlikely given how often we will be measuring your glucose levels. You will not be able to eat throughout the procedure but you will be able drink water. You will be given a meal before you go home to ensure your blood sugars are satisfactory.

This part of the study is optional and you should indicate in box 16 of the consent form if you are happy to take part. If you do not want to take part in this study day it will not stop you from entering the trial.

4) Brain Scan and Appetite Assessment Days

A small group of participants (20 per treatment arm) have been asked to take part in the brain scan and appetite assessment days before and after treatment (fMRI). Please see separate patient information sheet for more information (*Participant Information Sheet. Additional Details: Brain Scan and Appetite Assessment Days*). This part of the study is optional and you should indicate in box 17 of the consent form if you are happy to take part. If you do not want to take part in this study day it will not stop you from entering the trial.

5) Doubly Labelled Water

A small group of participants (20 per treatment arm) have been asked to take part in the 'Doubly Labelled Water Sample' before, during and after 32 weeks treatment. Please see separate patient information sheet for more information (*Participant Information Sheet. Additional Details: Participant Urine Collection and Packaging & Handling Procedure for Doubly Labelled Water Samples at Home*). This part of the study is optional and you should indicate in box 18 of the consent form if you are happy to take part. If you do not want to take part in this study day it will not stop you from entering the trial.

This completes Part Three of the Information Sheet.

If you decide to take part and give consent for any optional study procedures these will be conducted in the same manner as the main trial as detailed in Part 2 above.

Thank you for taking the time to read and consider this information sheet.