LETTER OF INFORMATION AND CONSENT

STUDY TITLE	Sitagliptin for the treatment of non-alcoholic steatohepatitis in patients with type 2 diabetes
Protocol No.	
STUDY INVESTIGATOR	Dr. Tisha Joy Division of Endocrinology and Metabolism Department of Medicine, St. Joseph's Health Centre Room B5-107, 268 Grosvenor Street London, Ontario N6A 4L6
CO-INVESTIGATOR	Dr. Melanie Beaton Division of Gastroenterology Department of Medicine, University Hospital ALL-132, 339 Windermere Road London, Ontario N6A 5A5

INTRODUCTION

You are being invited to take part in a research study. Please read this document carefully before you sign it. If there are any words or statements in this document that you do not clearly understand, please ask the study doctor or research staff.

As a research participant, it is your right to know all the procedures that are to be done in this study. By knowing the potential risks and benefits, you can make a decision to participate or not. This letter of information describes the background, purpose, procedures, benefits, risks, discomforts and precautions of the study. It also describes the alternative procedures that are available to you and your right to withdraw from the study at any time.

You will receive a copy of this Letter of Information and signed consent form for your records.

Background and Purpose of the Study
Non-alcoholic fatty liver disease (NAFLD) is the leading cause of liver disease among adults in the Western world. The spectrum of NAFLD ranges from steatosis (fatty infiltration) with and without inflammation to steatosis with inflammation and thickening (fibrosis) termed non-alcoholic steatohepatitis (NASH). Approximately 50% of patients with type 2 diabetes (DM2) have NAFLD. Importantly, NAFLD has also been noted to be a risk factor for the development of heart disease.

Unfortunately, there are currently no medical therapies available for the treatment of liver disease from NALFD/NASH. Although weight loss can be helpful to improving liver disease, weight loss is often difficult to achieve and even harder to sustain. Given the increasing prevalence of NASH, therapies to improve NASH are required.

You are being asked to take part in this research study which will examine the effects of a marketed anti-diabetes medication called sitagliptin on patients with type 2 diabetes and NASH. In particular, this study will be evaluating whether sitagliptin is effective in improving this liver disease as well as documenting the effects of sitagliptin on body fat distribution, hormone levels, and markers of heart disease.

We hope to have a total of 20 individuals with type 2 diabetes and NASH enrolled in this study. The study is only being conducted at this site and the visits will take place at University Hospital and/or St. Joseph's Hospital.

Procedures
All visits will require that you are fasting for a minimum of 10 hours. You may drink water during the fasting period. You may eat once all test procedures for the visit have been completed.

<u>Screening Visit:</u>

At your screening visit, we will take a complete history and physical examination as well as blood work to determine whether you are eligible to participate and ensure that it is safe for you to do so. We will be taking blood for glucose and diabetes control, liver tests, kidney test, and blood count. If you have not been formally diagnosed with NASH, it will be important that you be screened for other causes of liver disease such as the hepatitis B and C virus infections, and hemochromatosis (an inherited disorder causing excess iron to accumulate in the body). Up to 3 tablespoons of blood will be drawn for these tests as part of standard of care.

However, if you already have a confirmed diagnosis of NASH and if you have had blood tests done for your diabetes control/glucose, kidney, liver, and blood count within the past 30 days, we will not be repeating these latter labs and you can start at study visit #1 if you are eligible and agreeable to participating.

You are eligible for the study if:

- You have had no changes to your diabetes medications for the last 3 months
- You have a diagnosis of NASH
- You have a 3-month sugar test 8.9% or lower
- You have never been on sitagliptin
- You have not been on rosiglitazone or pioglitazone for the past 6 months
- You have never been or are not currently on medications such as steroids, amiodarone, or methotrexate
- You are not currently on plavix or clopidogrel

The entire visit will take approximately 2 hours.

After the screening visit, if you are eligible and decide to participate, you will be required to have 3 study visits over a 6 month time period.

At your initial visit (Visit 1), all of the following information and measurements will be taken:

1. Your body weight, body mass index (BMI), height, waist and hip circumferences, and blood pressure and heart rate will be measured.
2. Women who are of reproductive age and not using contraception will undergo a urine pregnancy test.
3. If you have not had the following bloodwork done in the past 30 days, blood will be drawn to assess your diabetes control, hormone levels, liver and kidney tests, and markers of inflammation and risk for heart disease.
4. If you have not had a liver biopsy done within the last 2 years or cannot obtain the slides from the biopsy, a liver biopsy will be performed. A liver biopsy is a procedure in which a needle is inserted through the rib cage or abdominal wall and into the liver to obtain a sample for examination. The physician will numb the area over the right lower part of the chest where the liver biopsy will be done. During the biopsy, a special needle device is used to remove the sample of your liver. You may also be asked to have a non-invasive exam of your liver (ultrasound) performed. Your study doctor will discuss this with you.
5. We will use a machine called Fibroscan, which looks very much like an ultrasound, except that its probe will be painlessly measuring the thickening or fibrosis within your liver.
6. After all of the above testing has been done, we will take a taxi to Robarts Research Institute, where we will use Magnetic Resonance Imaging (MRI) to produce pictures of the fat tissue in your liver, stomach and leg regions. In this study, the 3.0T scanner will be utilized. 3.0 T MRI scanners have been used for many years now for imaging in Canada.

The MRI machine uses a strong magnet and radio waves to make images of the inside of the body. You will be asked to lie on a long narrow table for 45-60 minutes in the MRI scanner while the machine gathers data. During this time, you will not be exposed to x-rays, but rather a magnetic field and radio waves. You will hear repetitive tapping noises that arise from the gradient coil around your body. We will provide earplugs. The space within the large magnet in which you lie is somewhat confined. We will be able to see you. So, if you have any problems while the MRI is being performed, the technologist or a member of the research team will be able to assist you.

In some circumstances, it may not be possible to schedule both the liver biopsy and MRI at the same visit. We will do our best to accommodate these two procedures such that a maximum of 14 days occurs between the two dates. If all procedures are done on the same day, the entire time for this visit will be 3 hours. Once all baseline procedures are completed, you will be randomized (like the flip of a coin) to receive either the study medication (sitagliptin) or an identical looking placebo (containing no active medical ingredients). "Randomized" means that you have a 50/50 chance of receiving either the study medication or placebo for the entire 6 month duration of the study. Neither you nor the investigators know who is taking the study medication and who is taking placebo. However, in the case of an emergency, the investigators would be able to find out what treatment you are receiving.

At your second visit (Visit 2), all of the following information and measurements will be taken:

1. Interim history and physical examination, including documentation of side effects and glucose control, blood pressure, heart rate, weight, BMI, waist and hip circumferences.
2. Women who are of reproductive age and not using contraception will undergo a urine pregnancy test.
3. Blood totaling 28 mL (under 2 tablespoons) will be drawn to assess your diabetes control, hormone level, liver and kidney tests, markers of inflammation and risk for heart disease.

Your entire visit will take approximately 90 minutes.

At your third visit (Visit 3), all of the same procedures as in Visit 1 will be done. We will document any side effects as well as examine your level of glucose control. Importantly, you will be having a liver biopsy at this visit. This second biopsy is not part of standard of care but is being done for research to document the effects of sitagliptin on your NASH. Again, as in visit 1, it may not be possible to schedule both the liver biopsy and MRI at the same visit. We will do our best to accommodate these two procedures such that a maximum of 14 days occurs between the two dates. If all procedures are done on the same day, the entire time for this visit will be 3 hours.

Who should not have an MRI?

If you have any history of head or eye injury involving metal fragments, if you have some type of implanted electrical device (such as a cardiac pacemaker), if you have severe heart disease (including susceptibility to heart rhythm abnormalities), you should not have an MRI scan unless supervised by a physician. Additionally you should not have a MRI scan if you have conductive implants (implants that can pass electricity or heat) or devices such as skin patches, body piercing or tattoos containing metallic inks because there is a risk of heating or induction of electrical currents within the metal element causing burns to adjacent tissue.

There may be reasons why you are not allowed to take part in this study. Some of these reasons include:

- You are participating in another research study
- You are pregnant or breast-feeding a child
- You desire to become pregnant in the near future
- You have a personal history of kidney disease or heart failure
- You have a history of alcohol or drug abuse

The study doctor or staff will discuss these and any other reasons why you may not be allowed to enter this study.

What benefit could there be from taking part in the study?
It is hoped that this study will help provide significant information regarding the use of sitagliptin as a potential therapy for NASH. However, this cannot be guaranteed. Importantly, information learned from the study may help other people in the future.

Risks and Discomforts
Sitagliptin is a marketed medication for the treatment of type 2 diabetes in Canada. It is well-tolerated with minimal side effects. It is not associated with weight gain; in fact, sitagliptin is considered weight neutral. Side effects include stuffy or runny nose and sore throat, occurring in less than 10% of individuals. However, the worrisome but very rare side effects of sitagliptin (occurring in less than 1% of individuals) include anaphylaxis (a severe allergic reaction), severe skin reactions such as Stevens Johnson syndrome, or inflammation of the pancreas (pancreatitis) which may be severe and lead to death. Stop taking your study medication and call your doctor right away if you have a generalized rash or hives or a pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen through your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.

Drawing blood from your arm may cause pain, bruising, lightheadedness, and rarely, infection. Blood samples specifically for this research study will be taken

along with blood tests done as part of your routine care. The research-related blood samples will total 63.5 mL, taken over the 6 months of the study.

During the procedure for the liver biopsy, a slight stinging sensation may be felt as the numbing medication is injected. After the procedure, approximately one quarter of patients may experience some discomfort at the site of the puncture. This includes some radiating pain to the shoulder which tends to be mild and brief. Serious complications are very rare (less than 1-3 in 1,000), and include internal bleeding, injury to internal organs and infection.

Part of your participation in this study will involve an MRI, which is a common medical diagnostic tool that uses a strong magnetic field, a low frequency magnetic field, and a radio frequency field. No X-rays are used. As with any technology there is a risk of death or injury. For MRI the risk of death is less than 1 in 10 million and the risk of injury is less than 1 in 100,000. These risks do not arise from the MRI process itself, but from a failure to disclose or detect MRI incompatible objects in or around the body of the subject or the scanner room. It is therefore very important that you answer all the questions honestly and fully on the MRI screening questionnaire.

Almost all the deaths and injuries related to MRI scans have occurred because the MRI operator did not know that surgically implanted metal hardware (such as a cardiac pacemaker) was present inside the subject during the MRI scan. Other remote risks involve temporary hearing loss from the loud noise inside the magnet. This can be avoided with ear headphone protection that also allows continuous communication between the subject and staff during the scan.
For comparison, the risk of death in an MRI is similar to travelling 10 miles by car, while the risk of injury during an MRI is much less than the risks associated with normal daily activities for 1 hour.

You may not be allowed to continue in this research study if you are unable to have a MRI scan because, for example, you have some MRI incompatible metal in your body, you may be pregnant or attempting to become pregnant, or you may have a drug patch on your skin that contains a metal foil. Should you require a medically necessary MRI scan in the future, the final decision as to whether you can be scanned will be made by a qualified physician considering all the risks and benefits.

Will the information collected be confidential?
All your information from this study will be kept confidential, available only to Drs. Joy and Beaton and their designated research team. If you decide to be in this study, the research team will collect information that identifies you. This may include your name, address, phone number, date of birth, medical history and medical-related information which shall be collected from your family doctor (or other health care providers) with your permission during your study visits. When

the results of this study will be published, no identifying information will be included.

This letter of information and consent form also serves to describe your privacy rights and if signed, will constitute your consent for the collection, use and disclosure of your personal information in the context of the study. Representatives of the University of Western Ontario Health Sciences Research Ethics Board may contact you or require access to your study-related records to monitor the conduct of the research.

You may take away your permission to collect, use and share information about you at any time by informing the study doctor. If you do this, you will not be able to stay in the study. No new information that identifies you will be gathered after that date. However, the information about you that has already been gathered may still be used. Some of the blood taken during the study will be saved and stored by Dr. Joy's research team until the study is completed. Once completed, blood samples will be disposed of according to laboratory standards and no samples will be kept for future use.

What are the costs of participating?
The costs of all procedures, examinations and medical care required as part of this study will be provided to you at no cost. You will be reimbursed a total of $300.00 for the entire study, which you will receive as $100.00 for each of the 3 study visits to cover any costs as a direct result of taking part in this study. If your expenses directly resulting from your study visit exceed the above specified amount (for example bus or train fares), please keep all relevant receipts and hand them to your study doctor at your visit and you will be reimbursed accordingly. If you only attend the screening visit, you will not be compensated financially.

Voluntary Participation
Participation in this study is voluntary. You may refuse to participate, refuse to answer any questions or withdraw from this study at any time with no effect on your future care. You do not waive any legal rights by signing the consent form. If you do decide to take part, the research staff will review this letter with you and ask you to sign the consent form and initial each page of the Letter of Information.

Can you leave the study before you have completed all of the visits?
Yes. Your participation in this study may be ended at any time.

Alternatives to Study Participation
If you decide not to participate in this study, this will not affect the standard of care you receive. Your study doctor will discuss the benefits and disadvantages of alternative treatments if applicable. Also, if new information becomes available that would influence your participation in this trial, we will inform you.

What happens now?
You are free to choose whether or not you want to take part in this study. You may talk with family members or friends before you make your decision. If you do wish to take part in this study, tell your study doctor and he or she will make all the arrangements.

Please ask the study doctor or research staff any questions about the study, to make sure you are aware of what will happen if you agree to take part. Please keep a copy of this Letter of Information and Consent form.

Who should you contact if you need more information?

In case you have questions about the study or the study drug, please contact:

Dr. Tisha Joy at 519-646-6296

If you have any concerns or complaints about your rights as a research participant or about the conduct of the study, you may contact:

Dr. D. Hill, Scientific Director, Lawson Health Research Institute
519-646-6100 extension 64672

CONSENT FORM

STUDY TITLE: Sitagliptin for the treatment of non-alcoholic steatohepatitis in patients with type 2 diabetes

I have read the Letter of Information, have had the nature of the study explained to me and I agree to participate. All questions have been answered to my satisfaction. I will receive a copy of this signed and dated Letter of Information and Consent.

_____
Participant's Name printed

_____ _____
Participant's Signature Date

_____
Investigator's Name printed

_____ _____
Investigator's Signature Date

_____
Printed name of person responsible for obtaining consent of participant

_____ _____
Signature of person responsible for obtaining consent of participant Date

STUDY TITLE: Sitagliptin for the treatment of non-alcoholic steatohepatitis in patients with type 2 diabetes

Primary Care Physician/Specialist Notification Option

The health information collected during this study will be used only for the purposes of the research study, as well as any subsequent analyses related to it. If you would like us to notify and share the health information collected on you with your primary care physician or your specialist, please indicate below.

_____Yes, I want the study doctor to inform my primary care physician/specialist of my participation.

_____No, I do not want the study doctor to inform my primary care physician/specialist of my participation in this study.

_____I do not have a primary care physician/specialist.

_____The study doctor is my primary care physician/specialist.

Primary Care Physician Name: _____

Specialist Name (if applicable): _____

If you are not eligible for participation in this study, would you be interested in participating in future research trials.

□ Yes □ No