CONSENT FORM: TIDE TRIAL

Thiazolidinedione Intervention with Vitamin D Evaluation (TIDE)
Sponsor: GlaxoSmithKline Inc

Study Title

Thiazolidinedione Intervention with Vitamin D Evaluation (TIDE). A Multicenter Randomized Double-Blind Placebo-Controlled Trial of a Thiazolidinedione (TZD) or Placebo and of Vitamin D or Placebo In People With Type 2 Diabetes at Risk For Cardiovascular Disease (AVD 111960)

Principal Investigator

(Insert local principal investigator info here)

Introduction

You are invited to take part in a research project. You have been considered because you have type 2 diabetes and other characteristics that increase your future chance of having a heart attack or stroke. It is important that you read the information about the study. You need to understand what you will be asked to do if you decide to be in the study. You also need to understand the possible risks of participation. If you do decide to participate, you will need to sign this form, which states that you have given your consent to participate. Feel free to discuss this with your family, friends, and your doctor before you make your decision. You can take as much time as you like.

Purpose

People with type 2 diabetes are at risk of having a heart attack, stroke and even death. They are also at risk for broken bones and some cancers. Some studies suggest that a class of diabetes drugs called thiazolidinediones (TZDs) and/or vitamin D may lower the chance of some or all of these diseases occurring. Other studies have suggested that the TZDs rosiglitazone or pioglitazone may increase the risk of some or all of these outcomes. This study will compare adding a TZD (either rosiglitazone or pioglitazone) to adding a placebo (a pill with no active ingredients). The effects of these study drugs, both good and bad, on the chance of heart attacks, stroke and death will be studied. It will also compare adding vitamin D to adding a vitamin D placebo to see if vitamin D can reduce the number of deaths or cancers requiring hospitalization, chemotherapy or surgery.

The study will be done in about 30 countries around the world and will include about 16,000 women and men. The study protocol and this consent form have been carefully reviewed and approved by an independent review board or ethics committee at every site in the world that is now actively recruiting participants. These committees are set up to protect the rights and well being of people participating in research projects like this one.

Study Procedures to be Followed

If you agree to be considered for this study, you will be asked questions about your health history and medication use. Your weight, height, body fat, blood pressure, heart rate, and waist and hip circumference will be measured. Blood and urine will be collected. You will have up to 30-45 cc (1-1.5 oz, or 2-3 tablespoons) of blood drawn at the first visit (screening) after fasting 8 hours. Fasting is when you don't have anything to eat or drink except water. If you do not fast before your scheduled visits, you will have to return at another time when you have fasted. The blood samples that are drawn will be used to check your blood sugar levels, kidney and liver function, and dietary fat levels in your blood. A pregnancy test (if needed) will also be done if you are a woman who is capable of conceiving. In addition, blood and urine samples will be stored and may be used to

measure various risk factors or risk markers for obesity, heart disease, disease of the blood vessels, cancers and other chronic diseases.

If you are eligible to participate, you will be scheduled for the run-in visit or the investigator may decide to combine this with your first visit. If you are currently taking either pioglitazone or rosiglitazone you will be asked to stop taking the medication while you are taking the TZD study drug. During the 3-week run-in period you will take 1 tablet of TZD study drug by mouth which could be either rosiglitazone or placebo and 1 tablet of vitamin D study drug by mouth, which could be vitamin D or placebo. If vitamin D study drug is not available when you enter the run-in, you will only take the TZD study drug. If after 3 weeks, either you or the study staff thinks that you are unable to tolerate the pills or participate in the rest of the study, you will be excluded. You will be asked to return all unused drug.

If you successfully complete the run-in period and agree to participate you will be scheduled for a randomization visit. At this visit you will be provided with either rosiglitazone (4 mg daily), pioglitazone (30 mg daily) or a placebo. At the same time or when available you will also be provided with either vitamin D (1000 IU daily) or placebo. Which study drugs you are provided with will be decided by chance using a computer. You have a slightly higher chance of taking placebo compared to rosiglitazone or pioglitazone. For example, in 100 patients participating in this study, 30 will receive rosiglitazone, 30 will receive pioglitazone and 40 will receive placebo. You will have the same chance of taking vitamin D or placebo (like the flip of a coin). Neither you, the research coordinator nor your doctor will know if you are taking active drugs or placebo(s). If there is an emergency, your physician can find out what treatment you are taking. At the randomization visit we will perform a simple test that measures the electrical activity of the heart called an electrocardiogram or ECG, and ask you to do a simple visual test. At this visit and at every future visit we will discuss ways to improve your health with lifestyle changes. At the randomization, 2-year and final visits you may also be asked to complete questionnaires that measure your quality of life, your thinking processes and your erectile function if you are male.

After the randomization visit, you will return to the study center after 1 month, 2 months, 6 months and then every 6 months. Participants will be asked to take the TZD study drug for up to approximately 5 years and the vitamin D study drug for up to approximately 5 years and potentially up to 10 years. We may also call you between visits to remind you to take your medications, answer any questions you may have, review your study medications and check on any side effects. It is important that you bring all of your study medications to each visit. At each visit you: a) will be asked about your health, your medications and any side effects; b) may have your blood pressure, heart rate, weight, height, and waist and hip measurement recorded and c) may be given a new supply of study drugs. You will have approximately 5-15 cc (1-3 teaspoons) of blood drawn at the 2-month visit. The same amount of blood will be drawn at the yearly visits to check your glucose, A1C and calcium levels after 8 hours of fasting.

At the 6 month or 1-year visit, the dose of your TZD drug will be increased (to 8 mg for rosiglitazone, or 45 mg for pioglitazone) if your study doctor thinks it is appropriate.

At the 2-year and final visits, you will also a) have an ECG; b) a simple visual test c) supply a first morning urine sample; and d) have up to 30-45 cc (1-1.5 oz, or 2-3 tablespoons) of blood drawn after 8 hours of fasting. Some of the blood and urine samples will be stored and may be used to measure various risk factors or risk markers for obesity, heart disease, disease of the blood vessels, cancers and other chronic diseases. Your blood sugar levels, kidney and liver function will also be checked.

Breast feeding and pregnant women are not allowed to take part in the study. If you are a woman who is able to have children, you need to use a reliable form of birth control (either the birth control pill, hormonal injections or implants, an intrauterine device, or a combination of spermicide and

condoms) to prevent any pregnancy during the study. If you become pregnant despite these precautions you will immediately notify the study team.

Long-Term Follow-Up

After the trial is complete and you have finished taking all the study medication, you may be contacted either by mail or telephone and asked to participate in a longer-term follow-up study.

To make it easier to contact you during the long-term follow-up, we will give your contact information to the Population Health Research Institute (PHRI) at Hamilton Health Sciences, McMaster University. The PHRI will only use this information for the purposes of contacting you regarding this follow-up. All your personal information will be kept in confidence and will not be given to anyone within the provisions of the law. If you do not agree to participate in the long-term follow-up, you can still participate in the trial. If you agree, we will also ask you to give us information that will allow us to use hospital and government databases to track whether you have been in hospital and why and the health care services you have used for up to 5 years after the completion of the trial, without having to contact you directly. In order to use this information, we would require your health card number or social insurance number. It is your choice to provide us with this information, but it helps us to know about your health status.

Possible Side Effects, Risks, and Discomforts

The study medications may cause some known side effects. In addition, there may be some side effects that have not been identified so far. Every measure will be taken to identify possible side effects as well as any benefits of the study pills. You must therefore notify the study staff of any changes in your health, newly started pills from the pharmacist and over-the-counter drugs, and symptoms you may notice (even if you think these changes or symptoms are not related to the study medication).

Side Effects Reported with Thiazolidinediones (Rosiglitazone and/or Pioglitazone)

Rosiglitazone is the active ingredient in Avandia and pioglitazone is the active ingredient of Actos. Some people who have taken rosiglitazone or pioglitazone had the following side effects:

- Fluid retention which may lead to swelling (for example ankle swelling), weight gain and rarely heart failure and difficulty breathing
- Swelling of the face, lips, mouth, tongue, or throat, which may cause difficulty in swallowing or breathing (angioedema)
- Decreased or blurred vision due to swelling (or fluid) in the back of the eye (macular edema)
- Anemia (low red blood cell count, which can cause fatigue)
- Increases in liver enzymes (which may indicate liver abnormalities)
- Modest increases in cholesterol
- Weight gain
- Low blood sugar (hypoglycemia) which may occur if a thiazolidinedione is taken with other diabetes medications
- Hives or rash (which may be itchy)
- Bone fractures especially in women and in the hand, upper arm, or foot.

Some people who have taken pioglitazone also had the following side effects:

- Erectile dysfunction
- Joint pain
- Flatulence (passing gas)

Some people who have taken rosiglitazone also had the following side effects:

- Constipation
- Increased appetite

GlaxoSmithKline (GSK) has analyzed heart safety data from their studies previously conducted in patients with diabetes. The results suggested that rosiglitazone might increase the chance of a heart attack especially in the presence of insulin or nitrate medication. However, other studies have not confirmed this observation.

During the study, if you get chest pain or chest tightness, or you feel chest pain more often or chest tightness, please get urgent medical attention and tell your study doctor at your next visit. You should also do this if you become short of breath or have trouble breathing (especially when you lie down), or if you gain weight quickly or notice swelling of your limbs.

One of the inactive ingredients in rosiglitazone and pioglitazone is lactose. You should tell the study doctor if you have severe lactose intolerance.

If important new information develops during the study, which may relate to your willingness to continue participation it will be provided to you in a timely manner.

Side effects reported with vitamin D

Some people who have taken vitamin D can have the following side effects:

- An allergic reaction (swelling of tongue, lips or throat, hives or itchy rash)
- Constipation
- Nausea, vomiting or decreased appetite
- Increased thirst and/or urination
- Muscle weakness
- Confusion
- Kidney stones

Use of Other Medicines and Possible Drug Interaction

It is important to tell the study staff about all other drugs you are taking, including those obtained without a prescription.

Monitoring of Safety During the Study

An independent group of people who are not otherwise involved in this study will regularly review the safety of people participating in this study as well as information regarding the safety of rosiglitazone, pioglitazone, vitamin D from other sources. This group may recommend changes to the study (or even early stopping of all or part of the study) based on their review of this information.

Other Potential Risks

When blood samples are taken, you may have some discomfort (brief pain) or develop some bruising or very rarely, a minor infection where the needle went in. Every precaution will be taken to prevent infection. Some people feel dizzy when they have blood drawn, but this goes away when the person lies down.

An ECG is painless. When first applied, the disks may be cold and in rare circumstances, you may develop a localized rash or irritation where the patches are placed.

Possible Benefits of Participation

Taking part in this study may or may not make your health/condition better.

The information obtained from your participation in this study may help us understand more about whether the drugs being studied can increase or reduce the risk of cardiovascular and chronic diseases.

You will receive some counselling regarding a healthy lifestyle, and will receive all of your study medications free of charge.

Proven Ways to Prevent Cardiovascular Disease and Lower Glucose

Several studies have now shown that you may lower your risk of heart attacks, strokes or cardiovascular death by several approaches. These include: a) drugs that lower blood pressure; b) statin drugs that lower cholesterol; c) ACE inhibitor drugs; d) aspirin and e) beta blocker drugs. You will be permitted to take any of these drugs during the study and, depending on your medical condition, one or more of these drugs may be prescribed by your usual physician. Studies have also shown that there are many alternative ways of lowering blood sugar levels in people with diabetes and you will be able to take any of these drugs (except for a TZD) during the study, depending on the judgment of your physician.

Compensation

The study medication and clinic visits will be provided free of charge. No compensation will be provided for your participation. You and your health insurance company / the National Health Services will continue to pay for your regular health care.

Study Sponsor:

GlaxoSmithKline is a company that creates and makes medicines and other health products. It is also called "GSK".

GSK pays the study doctor and ***<institution>*** to run this study.

Information about this study is confidential. We ask that you keep it private. You can discuss this information in private with your doctor or family to talk about your healthcare or to decide about taking part in this study.

As the sponsor, GSK will be the owner of the study results. GSK plans to use the results and may get patents or make profits other ways. You will not be paid any part of this.

Liability

GSK will pay your out-of-pocket costs (not covered by insurance) for reasonable and necessary care if you are hurt by the study drug or a procedure that is done to you only because you are part of this study.

Signing this consent form does not change any legal rights you may have.

Right to Withdraw or Stop Study Medication

Participation in this study is voluntary. Should you decide not to take part in this study your health care treatment will not be affected by this decision. Refusal to participate will not affect any benefits you are entitled. If you decide to take part in the study, you will need to sign this form, which says

that you have consented to participate. If you agree to participate, you may withdraw from the study at any time without affecting any benefits to which you are entitled, although it is advisable to tell the investigator if you intend to do this. You have the right to withdraw from the study completely (this means you do not wish to be contacted by any study staff after you withdraw) or you may just wish to stop one or both of your study medications, but will allow study staff to contact you to see how you are doing. If you stop taking any of the study medications for any reason during the study, we will ask you to return any leftover drug. However, even if you are no longer taking the study medications, the information you are providing is still very important for the study and you will be asked to continue attending regular study visits or allow the staff to contact you or a family member by phone.

It is very important for the success of the study that we are able to collect information on you throughout the duration of the study. If you agree to participate, you are giving permission for your doctors to provide information about your health, in confidence, even if you do not wish to be contacted again by any study staff. If you agree, we will also ask you to give us information that will allow us to use hospital and government databases to track whether you have been in the hospital and why and the health care services you have used for up to 10 years. This information will be collected even if you decide to withdraw from the study and do not wish to be contacted again by any study staff after you withdraw.

Any important new information that develops during the course of the study, which may relate to your willingness to continue participation, will be given to you or your legally acceptable representative in a timely manner.

GSK (the study sponsor), the steering committee, the regulatory authority, or the study doctor may choose to stop the study drugs or your participation in the study if:

- The results of certain tests show that you are not right for this study or for the study drug.
- You get any new health problems during the study
- You get pregnant or decide that you want to become pregnant
- The study doctor thinks it is in your best interest to stop.

There may be other unexpected reasons your participation in the study is stopped. If this should happen, you will be made aware of the reason at that time. However, even if one or both of the study drugs are stopped you will still be followed in the study.

Confidentiality

During your participation in this clinical study the research staff will collect personal information (such as name and address) and information related to your health. Your collected data will be reported to the Population Health Research Institute at Hamilton Health Sciences, McMaster University who are performing this study. The Project Office at Hamilton Health Sciences will process your data with electronic data processing systems. In the electronic database, your data will be identified with a code number and your initials. If you decide to take part in the study, your information will be stored in this way until the study is over, including the length of time that we must keep records about the study.

The data will be analyzed in order to determine the effectiveness and safety of rosiglitazone or pioglitazone or vitamin D, as well as for general health research. Your data may be shared with GSK and others including local and foreign drug regulatory agencies who oversee drugs like rosiglitazone or pioglitazone or vitamin D and may be used in scientific publications. Your data may also be forwarded immediately to local and foreign drug regulatory agencies in case you suffer an adverse reaction to any of the study drug.

The data may be shared with other companies or universities to better understand diabetes or to further develop the study drugs or other drugs. The data may be used to help plan new studies. Your name will not appear in any of these reports.

Representatives of the Project Office at Hamilton Health Sciences, GSK, the independent ethics committee/institutional review board, or local or foreign regulatory authorities, and others working with GSK or Hamilton Health Sciences, may directly access your medical records at your doctor's site in order to determine the accuracy of the reported data. These representatives will observe professional secrecy and keep your identity confidential to the extent permitted by law. You have the right to see your study data at your doctor's office, and to request corrections of any data that are wrong.

You will be given a copy of this informed consent document and may ask for additional information, at any time during the study, from †‡ **(insert name and telephone number of investigator)**. You may also contact †‡ **(insert name and telephone number)** if you have questions about your rights as a research subject. Contact **(insert name and telephone number of investigator)** if you think you have been hurt from taking part in this study, or have any questions about side effects.

Personal and medical information about you will be kept confidential. It will be kept in a secured file.

Study information about you that is not helpful to your health care will not be given to you or others. This means that no one (not you, your family, your doctor, your insurance company, or your employer) will have access to this information during or after the study.

If you have a serious event that it not expected and is related to the study drug, regulatory agencies and other clinical investigators may be informed about the event and which treatment you are on. Your name and contact information will not be disclosed and you will only be referred to by a code number.

When you sign this consent form, you agree to have your personal and medical information used as described here.

I have read, or had read to me, the informed consent document for this trial. By signing below I show that:

- I have read this form, and the study has been explained to me
- I have discussed the study and asked questions. I am satisfied with the answers
- I have had time to make my decision
- I freely agree to take part in the study described in this form
- I have been given names of study staff whom I can call
- I agree that GSK, study staff, and others may have access to my medical and personal information as described in this form
- I agree that my information may be shared with people who are not healthcare providers and that the information would no longer be protected by Health Insurance Portability and Accountability Act HIPAA.
- I agree that the study doctor may tell my doctor that I am taking part in this study.
- I agree to take part in this trial and to follow all study procedures as detailed above.

1. I agree to provide my health card number or social security number for linkage and tracking purposes

   ☐ **YES** Please provide your health card or social security number here: _____ ☐ **NO**

2. I agree to have my contact information sent to Hamilton Health Sciences to be used and stored in a confidential manner

   ☐ **YES** ☐ **NO**

3. I agree to continued participation in the long term follow-up study (for up to 10 years)

   ☐ **YES** ☐ **NO**

If you mark "no" to questions 1, 2, or 3you may still participate in the trial.

Last name: _____ **First name:** _____
(block letters) **(block letters)**

Signature: _____ **Date:** _____
(to be completed by participant at time of consent)

(Where required) [In Countries that do not require a witness the following lines for witness should be deleted before submitting the consent to the ethics committee; note the signature of the investigator]

Witness
Last name: _____ **First name:** _____
(block letters) (block letters)

Signature: _____ **Date:** _____

Investigator/Sub-investigator or person who conducted the Informed Consent discussion

I confirm that I have personally explained the nature, purpose, duration, and foreseeable effects and risks of the trial to the subject named above.

I have carefully explained the nature of the above research study to the participant. I hereby certify that to the best of my knowledge, the person signing this consent form understands the nature, demands, benefits, and risks of participating and that his/her signature is valid. A medical problem or language or educational barrier has not precluded this understanding.

Last name: _____ **First name:** _____
(block letters) (block letters)

Signature: _____ **Date:** _____

A signed and dated copy of this document shall be given to the person signing this form.