INFORMED CONSENT DOCUMENT

STUDY TITLE: Targeting Inflammation With Salsalate in Type 1 Diabetes Neuropathy-TINSAL -T1DN

NCT NUMBER: NCT02936843

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UNIVERSITY OF MICHIGAN

CONSENT TO BE PART OF A RESEARCH STUDY

INFORMATION ABOUT THIS FORM

You may be eligible to take part in a research study. This form gives you important information about the study. It describes the purpose of the study, and the risks and possible benefits of participating in the study.

Please take time to review this information carefully. After you have finished, you should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or other doctors) about your participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.

1. GENERAL INFORMATION ABOUT THIS STUDY AND THE RESEARCHERS

1.1 Study title:

Targeting Inflammation with Salsalate in Type 1 Diabetes Neuropathy-(TINSAL-T1DN STUDY): A phase II/III, single-center, randomized, double-blind, placebo-controlled clinical trial

1.2 Company or agency sponsoring the study:

The National Institutes of Health

1.3 Names, degrees, and affiliations of the researcher conducting the study:

Rodica Pop-Busui, MD, PhD, Department of Internal Medicine, Division of Metabolism, Endocrinology and Diabetes

2. PURPOSE OF THIS STUDY

2.1 Study purpose:

The investigators want to learn if treating someone with a medication called salsalate can improve neuropathy caused by diabetes. Specifically, the investigators also want to learn if treatment with salsalate increases the number of small nerve fibers in the skin and reduces inflammation at the nerves. This information will help the investigators to find out whether salsalate can help reduce painful symptoms of neuropathy in people with type 1 diabetes. Salsalate is an anti-inflammatory drug in the salicylate class and is similar to aspirin. Salsalate is commonly used as a medication for arthritis. The investigators believe that the anti-inflammatory properties of salsalate could also help painful neuropathy symptoms.

3. INFORMATION ABOUT STUDY PARTICIPANTS (SUBJECTS)

Taking part in this study is completely **voluntary**. You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

3.1 Who can take part in this study?

The table below summarizes the information about who can and who cannot be in the study. The study staff will review all of these with you and may look at your medical record to find out more about you. This is to make sure that it is safe for you to be in the study, and to make sure that the study is conducted properly.

<u>You may be able to be in the study if:</u>

- You have type 1 diabetes
- You have mild peripheral neuropathy. Tests of your nerves and other examinations will be done to find out if you meet the criteria for this study.

- You are 18 to 70 years old.
- You are on a stable insulin treatment program for at least the past 3 months.
- You are willing and able to take an oral (by mouth) medication 3 times per day for 12 months.
- If you take daily aspirin, or daily non-steroidal anti-inflammatory medications, you are willing and able to not use these medications during the time that you are in the study. Daily low-dose aspirin (81 mg per day) may be continued.
- If you are a woman and of child-bearing potential, you are willing to use an appropriate method of contraception during the course of the study. These include oral contraceptive pills, use of an IUD, other chemical contraception (e.g., norplant or depoprovera), or surgical treatment that would prevent pregnancy (e.g., tubal ligation or hysterectomy).

You cannot be in the study if:

- You have neuropathy from a cause other than diabetes.
- You are allergic to salsalate or similar medications (including aspirin and other non-steroidal anti-inflammatory medicines like ibuprofen and naproxen).
- You are currently being treated with blood thinning agents such as Coumadin, Plavix, Pradaxa, aspirin (more than 81 mg daily). The study team will review all your medications
- You have had any severe low blood sugar in the past 6 months that resulted in coma or seizure.
- You have a history of recurrent diabetic ketoacidosis (DKA) or have had any occurrence of DKA within the last three months.
- You have severe neuropathy, had an amputation or have an active ulcer on either foot or either leg. You may be able to participate if you had one or more toes amputated due to a condition other than neuropathy (e.g., severe injury).
- Your creatinine level (a measure of kidney function) is greater than 1.4 mg/dl (for women) or greater than 1.5 mg/dl (for men) or your estimated GFR is under 60.
- You have elevated levels of albumin in your urine or other signs of reduced kidney function
- You have ever had an organ transplant (such as lung, kidney, heart, pancreas, liver, bone marrow).
- You have abnormal liver function tests (greater than 2.5 times the upper limit of normal for SGOT and or SGPT, greater the 1.5 times the upper limit of normal for bilirubin), or if you have active hepatitis C.
- You have a low blood platelet count (platelets < 100,000)
- You are on chronic immunosuppressive therapy, for example, daily prednisone or other steroids, methotrexate, Imuran, CellCept. Use of inhaled steroids for management of asthma, however, may be acceptable.
- You have asthma associated with aspirin or NSAID-medications.
- You have a history of drug or alcohol abuse within the last 5 years, or if you take more than 10 alcoholic drinks per week.
- You have a history of gastrointestinal bleeding or active gastric (stomach) ulcer.
- You are being treated for any cancer (other than basal cell or squamous cell skin cancer).
- You are being treated with lithium.

- If you are a woman, you cannot be in the study if you are pregnant, nursing, or planning to become pregnant during the time of the study.
- You have developed keloid scarring in the past. Keloids are large, thick masses of scar tissue. These are more common among dark-skinned people.
- You are receiving other experimental treatments
- Presence of any condition that, in the opinion of the investigator would make it unlikely for you to complete 12 months of study participation, or make it unsafe for you to participate.

Let the study investigators know if you are, or believe that you may be allergic to lidocaine or epinephrine. These are used to numb a small area of skin during the skin biopsies. You may not be able to be in this study if you have severe allergies to either of these medications.

In addition, you cannot start the study if you currently have chicken pox, the flu, flu-like symptoms, or other symptoms of viral illness. Also, if you develop any of these conditions during the study, you should stop taking salsalate and contact the study team. This is because a serious illness called Reyes' Syndrome, that has been associated with taking aspirin during viral illness. Because aspirin and salsalate are similar, you should not take salsalate when you have a viral illness.

If you take a daily aspirin, or take daily non-steroidal anti-inflammatory medications (like Motrin or Aleve), you will be asked to stop using those during the study. If you are already taking once daily low-dose aspirin (81 mg), you may continue to take this during the study. Salsalate and other medications like it may be harmful to unborn children. Therefore, women of child-bearing age (pre-menopausal) must agree to use appropriate contraception (birth control) during the study. This includes use of oral contraceptives (birth control pills), implanted or injected contraceptives (e.g., Norplant; Depoprovera, IUDs), or surgical sterilization (tubal ligation, hysterectomy). All women will have a pregnancy test at the start of the study (before receiving study medication) and may be retested during the course of the study.

3.2 How many people (subjects) are expected to take part in this study?

We will enroll up to 70 people in this study.

4. INFORMATION ABOUT STUDY PARTICIPATION

4.1 What will happen to me in this study?

There are 7 "in-person" visits in the study.

At your first visit, the study staff will review the study with you, and review your medical history, (including information about your diabetes, your diabetes treatment and what medications you use) and perform physical exams to make sure that you qualify for the study. You will have your height, weight, blood pressure and pulse checked, much like a regular visit to the doctors. The study staff will ask you specific questions related to signs and symptoms of neuropathy. The study staff will do a foot examination that will include looking at your feet, checking your reflexes, checking how well you feel things like vibration (using a tuning fork), hot versus cold, sharp versus dull. Many of these tests are done as part of your routine diabetes care. The study staff will also review your recent laboratory tests, specifically looking at your kidney and liver function (Metabolic Comprehensive, Uric Acid), checking your blood counts for anemia or signs of infection (Complete Blood Count with Platelets), measure levels of inflammation (Cystatin-C) and diabetes control (HbA1c). We will also measure your level of thyroid hormone, and your cholesterol levels. Urine tests will be done to measure the amount of protein in your urine (Urine Albumin). If you haven't had these tests done at the University of Michigan within the last 3 months (one month for HbA1c, 6 months for Urine Albumin), we will do these tests. If you are a woman of childbearing age and potential, a urine pregnancy test will be done, regardless of contraceptive practices. These tests will be analyzed by the University of Michigan Health Systems clinical laboratories and the results will become part of your regular medical record. Blood draws will be done either by trained members of the study team or by clinical phlebotomists at the University of Michigan.

We will also collect a blood and urine sample for special tests of inflammation that are of interest to the researchers. These inflammatory marker tests will not be done by the University of Michigan clinical laboratories and you will not necessarily receive the results of these tests and results will not necessarily become part of your regular medical record. These special tests will be done either at your first visit (screening) or second study visit (baseline).

At the first visit you will have nerve conduction studies done to make sure that you are eligible for the study (to verify that you have neuropathy). Nerve conduction studies will be done on your arm and leg on your dominant side (the hand you write with). Nerve conduction studies take about 30 to 45 minutes to complete. You will experience a sensation like a carpet shock, or a snap with a rubber band repeatedly during the test. The test is not dangerous or harmful, but may be uncomfortable. The nerve conduction test will either be performed by a trained member of the study team or a clinical nerve conduction technician at the University of Michigan. You will be asked to complete questionnaires that ask about your symptoms of neuropathy and how your neuropathy affects your quality of life.

If you are eligible for the study based on the first visit test results, you will be scheduled for a baseline study visit. This will ideally be within 4 weeks of the screening visit but may be up to 180 days after the screening visit.

At the baseline visit, the study staff will take two samples of skin (skin biopsy). One sample is taken just above the outer ankle bone, and the other sample taken on the side of your thigh. Both samples are taken from the same leg. A local anesthetic (lidocaine and epinephrine) will be used to numb the area to be sampled. A small needle (the size of an insulin syringe) will be used to administer the anesthetic into the skin. Then, a small circle of skin will be removed using a tool that looks a bit like a very tiny apple corer. The diameter of the tool is 3 millimeters. For reference, the diameter of a typical pencil eraser is about 5 millimeters. Once the skin sample is removed a dressing will be placed on top of the wound and you'll be given instructions for how to care for the wound.

You will be asked to fast for the baseline visit so that tests can be done to measure your heart rate, blood pressure, and changes in heart rate and blood pressure in response to a number of activities, including lying quietly, slow deep breathing, standing and blowing into a tube. These tests are referred to as Heart Rate Variability, or HRV tests.

A series of questionnaires will be given to you to complete. These questions ask you about your symptoms of neuropathy and how they affect your daily life and your attitude and mood.

You'll be asked to perform several tests to measure your balance and mobility – these include standing with eyes open or closed, getting up from and back down into a chair, walking a short distance and lifting your feet, one at a time up to a step stool.

After the baseline visit a 3-month supply of study medication will be mailed to you, and you will be instructed about how to take it and what side effects to watch for. **The study medication will either be salsalate or a placebo. Each person enrolled the study will be assigned by chance. Slightly more people will be assigned to salsalate than to placebo. For every 3 people who are assigned to salsalate, 2 people will be assigned to placebo.** A placebo is a pill or tablet that looks just like the medication salsalate, but has no active medication in it. You will be asked to take up to a total daily dose of 3 grams of study medication; 1-gram (2-500 mg tablets) in the morning, 1 gram (2-500 mg tablets) mid-day and 1 gram (2-500 mg tablets) at night. You'll be asked to take your study medication with a meal or other food.

Remember that neither you nor the study team will know if the medication you are taking is salsalate (the active medication) or a placebo (a tablet with no active ingredient).

After the baseline visit, the study staff will call you or email you to check on how you are doing, to answer any questions you may have about the medication, and to ask if your skin biopsy sites are healing.

You will then be asked to come to the study clinic about 1 month after you start the study medication, two months after that, and then every three months until the end of the study (visit 7), about 12 months after the baseline visit. Most of the visits will only take 60 to 90 minutes. At each visit, you will be asked to report any

changes in your health, and may be asked to complete written surveys. Blood and urine samples will be taken at most of the visits. You will be asked to return any unused study medication, and a new supply will be mailed to you.

At your final visit (visit 7, about 12 months after starting study medication) the procedures that were done at screening and baseline will be repeated, along with blood, urine samples and two additional skin biopsies. You will need to fast for this visit, and the visit may take several hours to complete.

After the final visit (visit 7) you will no longer be taking the study medication. The study staff will contact you by phone or email, within a week of your final visit to find out how you are doing and how your biopsy sites are healing.

As a subject participating in this research study, you have certain responsibilities that may apply to this study, such as ensuring that you arrive at all of your scheduled appointments, take your study medication as directed, and report any adverse reactions you may have during the study.

4.2 How much of my time will be needed to take part in this study?

The screening visit (visit 1) will take 2 to 4 hours to complete. If more convenient for you, the screening visit can be completed in two shorter sessions on separate days. Visit 2 – the baseline visit will take 3 to 4 hours and you will be required to fast. Visit 3 will only take about 1 hour and does not require that you fast. Visit 4, 5, and 6 should take 60 to 90 minutes and do not require fasting. The final visit (Visit 7 will take 3 to 5 hours to complete and you will be required to fast. By fasting, we mean nothing to eat or drink except water, for 8 to 10 hours prior to the start of the visit.

During the study (from visit 2 to visit 7) you will need to take study medication 3 times daily.

4.3 When will my participation in the study be over?

Your participation will be over after you have completed visit 7 and we have contacted you by phone or email within a week after visit 7.

4.4 What will happen with my information and/or biospecimens used in this study?

With appropriate permissions, your samples and collected information may also be shared with other researchers, here, around the world, and with companies.

Your identifiable private information or identifiable biospecimens may be stripped of identifiers and used for future research studies or distributed to another researcher for future research studies without additional informed consent.

5. INFORMATION ABOUT RISKS AND BENEFITS

5.1 What risks will I face by taking part in the study? What will the researchers do to protect me against these risks?

The known or expected risks are:

There is time involved in the study. Each study visit will take from 60 minutes to 5 hours as described in section 4. There is the daily time you'll need to take the study medication.

Risks associated with blood collection are pain, discomfort, bleeding, bruising or infection. There is also the risk of dizziness, light-headedness, nausea or even fainting.

The risks associated with nerve conduction studies are the discomfort associated with these studies. Again, you may feel like you are getting repeated "carpet shocks" or that someone is snapping a rubber band against your skin. Other than the discomfort, this test is not harmful or dangerous.

You will be asked to fast (that is, have nothing to eat or drink except water) for several hours (about 8) prior to two of the visits when the HRV tests are done. Fasting may increase your chance of having a low blood sugar

reaction (insulin reaction or hypoglycemia). The slow-deep breathing, standing, and blowing tests that are part of the HRV testing may make you feel dizzy or lightheaded for a brief period of time.

The risks associated with the skin biopsies are pain, bleeding, bruising, or infection. You may also have a small scar or discolored area at the site of the biopsy. People with diabetes may have slow wound healing, so it is important for you to follow the study staff's directions regarding wound care after the biopsies. And, important for you to contact the study staff or your regular doctor if you have concerns about how the wounds are healing.

There is a risk to loss of privacy related to being in a research study. Please see section 9 of this document which discusses privacy concerns.

Risks associated with the study medication, salsalate:

Common side effects of salsalate are nausea, loss of appetite, heartburn and feeling of ringing in the ears and some degree of deafness. These effects usually subside as one continues the treatment but may require that your dose of salsalate be reduced. If you are experiencing what you think are side effects of the medication you should contact the study doctor or nurse. The dose of salsalate will be reduced to a level where you can tolerate any side effects that you are experiencing, or the medication will be discontinued.

Salsalate in high doses can cause gastrointestinal bleeding, especially in patients with a previous history of gastric ulcers. For this reason, you should also keep watch over the color of your stools. Black colored stools are an indication of gastrointestinal bleeding. If this happens, you should let the study team know and if you have bleeding, the medication will be stopped.

Salsalate increases the risk of bleeding in general, so you may be more prone to bruising, and to bleeding around your insulin injection or infusion sites. The risk of bleeding related to salsalate is increased when taken with other salicylate medications such as aspirin, or with other NSAIDS, such as ibuprofen, or with medications used to thin the blood (for example, Coumadin, heparin, Plavix).

Hypoglycemia (low blood sugar). Salsalate can lower blood sugar, so you should be checking your blood sugar regularly and should be prepared to treat a low blood sugar reaction, for example, by carrying glucose tablets or juice with you at all times. You may need to have your insulin dose adjusted while you are taking salsalate to prevent low blood sugars. The study team can help you with this, or, you may contact your regular doctor who helps you manage your diabetes for advice about adjusting your insulin dose.

Symptoms of hypoglycemia are:

- nausea
- extreme hunger
- nervousness
- sweating
- a rapid heartbeat
- numbness or tingling in the fingertips or lips
- trembling
- confusion
- blurred vision
- drowsiness
- very rarely, loss of consciousness or coma

Other risks associated with salsalate and similar medications.

There are some other things you should be aware of when taking salsalate, or other medications in the class known as NSAIDs (Non-steroidal Anti-inflammatory Drugs). The class includes aspirin, and common over the counter medications like ibuprofen (Advil®, Motrin®) and naproxen (Anaprox®, Aleve®).

- These medications can increase the risk for heart attacks or strokes, especially if taken in high doses over long periods of time. If you have chest pain, shortness of breath, weakness, slurring of your speech, you should seek medical attention right away.
- These medications can cause fluid retention and edema (swelling). You should report any increase in swelling (e.g., in your legs) to your health care provider and the study team.
- These medications can cause damage to the liver in some people. If you notice symptoms of nausea, fatigue, itching, jaundice (yellowing of the skin or eyes), pain in your upper abdomen and flu-like symptoms) you should stop taking salsalate and notify your health care provider and the study team.
- Some people may be allergic to these medications, and if you are allergic to one type of NSAID, it is more likely that you'll be allergic to others in the class. If you develop hives, itching, a rash, swelling, or difficulty breathing, you should stop taking the medication and get medical attention right away.
- Rarely, these medications can cause serious skin effects. If you develop a rash, or blisters on your skin, or fever or other "allergic" type symptoms, stop taking the medication and seek medical attention right away.
- These medications can change how certain blood pressure medications work. If you are taking certain diuretics (like Lasix) or ACE-inhibitors (such as lisinopril, or captopril), the doses may need to be adjusted while you are taking salsalate. You should also be alert to changes in weight or fluid retention (swelling of feet and ankles) while you are taking salsalate and report changes to the study staff or your regular doctor.
- A serious condition called Reyes' Syndrome has been reported when aspirin has been taken during viral illness, such as chicken pox or the flu. You should not take aspirin or salsalate if you have the flu, chicken pox, or other viral type illnesses.

Salsalate is not approved for use in pregnant or nursing women. If you are pregnant or nursing, or if you become pregnant while in the study, we do not know what the effects would be to you or your child, and there is some evidence that NSAID medications, including Salsalate, may cause harm to unborn children, especially late in pregnancy.

The researchers will try to minimize these risks by: We'll work with you to try to schedule your visits when it is most convenient for you. Sometimes, we are limited in our ability to be flexible with scheduling, based on availability of study staff and equipment.

Blood sampling will be performed by staff with skill and experience in venipuncture.

The nerve conduction studies will be done by study staff with many years of experience in performing these tests.

To reduce the chance of low blood sugar while you are fasting for the HRV tests, you may need to adjust (lower) your insulin doses. If you need advice about how to reduce your insulin doses, you should contact your regular doctor or the study staff. Also, if your blood sugar does go low before the test, treat it by eating something sweet (glucose tablets, juice, pop, lifesavers, etc.). Let the study team know and you may be asked to reschedule the test for another time, or the study team may delay the start of the test until your blood sugar has recovered.

If you feel dizzy or lightheaded during the HRV tests (or at any time) let the study staff know. The study staff will be close by during the tests to help you change positions safely.

The skin biopsies will be done by members of the staff who have experience in doing them. The areas biopsied will be cleaned with antiseptics prior to the biopsy and a local anesthetic used to reduce pain during the procedure. You'll be given information about wound care, and what symptoms to watch for and to report any

signs or symptoms of infection. The study staff will call you within a week of your biopsy to check on how it is healing.

Side effects of salsalate may be minimized by taking with food, so you'll be asked to take your salsalate at your meal times, or with a snack. If you develop symptoms such as nausea or loss of appetite, that doesn't resolve, we may ask you to reduce your dose, or stop the medication altogether. We may also reduce your dose, or stop it if you develop ringing in the ears (tinnitus) or feel that your hearing is reduced.

You need to be alert to signs of bleeding from the stomach or bowels, so you should pay attention to the color of your stools. Black colored stools are an indication bleeding from the stomach and bowel. If this happens, you should let the study team and your regular doctor know. If you are having bleeding, the medication will be stopped.

You need to tell the study staff about all medications or dietary supplements that you take so that we can be sure that it is safe for you to take salsalate.

Because there is an increased risk of bleeding when salsalate is combined with other drugs that thin the blood, you will be asked to stop using daily aspirin (a low dose of 81 mg aspiring per day may be continued) or other daily NSAIDS when in this study. If you aren't willing to do so, then you should not be in this study. You CANNOT be in the study if you are taking blood thinning agents such as Coumadin, heparin or Plavix.

Because salsalate can lower blood sugar you should check your blood sugar regularly and should be prepared to treat a low blood sugar reaction by carrying glucose tablets, fruit juice, or other forms of quick carbohydrate (sugar) with you at all times. You may need to have your insulin dose adjusted while you are taking salsalate to prevent low blood sugars. The study team can help you with this, or, you may contact your regular doctor who helps you manage your diabetes for advice about adjusting your insulin dose.

If you have any changes to your health or how well you feel while you are taking salsalate, you should stop taking the medication and contact a member of the study team, or contact your regular health provider. This is especially important if you have any of the symptoms like shortness of breath, chest pain, abdominal pain, skin changes (rashes, hives, swelling, blisters), weakness or dizziness. You should also report any yellowing of your skin or yellowing of your sclera (the white part of your eyes) as these can be signs of liver problems.

If you know that you are pregnant, or if you are nursing, you cannot be in this study. If you think that you might be pregnant, you may be asked to have a pregnancy test. If you are capable of becoming pregnant, we'll ask you to tell us what your plan for contraception during the study is. Acceptable forms of contraception are oral contraceptive pills, implanted or injectable contraception (e.g., norplant or depo-provera) IUDs, or surgical contraception (tubal ligation). If you think you have become pregnant and have started study medication, you should stop taking the medication and contact the study staff or your regular doctor as soon as possible. All women will have a pregnancy test at the start of the study (before receiving study medication) and may be retested during the course of the study.

Because drugs in the salicylate and the NSAID class can interfere with the actions of some blood pressure medications, like diuretics (e.g., Lasix) and ACE-Inhibitors (e.g., lisinopril), the study staff will check your blood pressure at each visit and may adjust the dose of your blood pressure medications. You should report to your doctor or to the study staff any change in your blood pressure control, or significant (more than 5 pound in one week) weight gain, or if you notice swelling in your feet or ankles.

If you think you are coming down with, or if you have the flu, if you develop chicken pox, or if you have other symptoms of a viral illness (such as fever, tiredness, body aches) you should stop taking the salsalate and contact the study staff as soon as possible. Flu shots are generally recommended for all people with type 1 diabetes, and the study staff will encourage you to have an annual flu shot.

As with any research study, there may be additional risks that are unknown or unexpected.

5.2 What happens if I get hurt, become sick, or have other problems as a result of this research?

The researchers have taken steps to minimize the risks of this study. Even so, you may still have problems or side effects, even when the researchers are careful to avoid them. Please tell the researchers listed in Section 10 about any injuries, side effects, or other problems that you have during this study. You should also tell your regular doctors**.**

5.3 If I take part in this study, can I also participate in other studies?

Being in more than one research study at the same time, or even at different times, may increase the risks to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the researchers involved in each study.

5.4 How could I benefit if I take part in this study? How could others benefit?

You may not receive any personal benefits from being in this study. We hope to learn whether we can find measurable differences in nerves found in skin after a 12 months of treatment with salsalate. The findings from this study will help the investigators develop a more detailed study to determine how well salsalate works for people with painful neuropathy.

5.5 Will the researchers tell me if they learn of new information that could change my willingness to stay in this study?

Yes, the researchers will tell you if they learn of important new information that may change your willingness to stay in this study. If new information is provided to you after you have joined the study, it is possible that you may be asked to sign a new consent form that includes the new information.

6. OTHER OPTIONS

6.1 If I decide not to take part in this study, what other options do I have?

You have the option to not participate in the study. *There may be other ways to treat your symptoms of neuropathy, including pain medicines and some anti-depressant medicines. Your doctor can tell you more about these other treatments, their risks and their possible benefits. You should have this discussion about the risks and benefits or other treatment alternatives prior to making your decision about whether or not you wish to take part in this research study.*

7. ENDING THE STUDY

7.1 If I want to stop participating in the study, what should I do?

You are free to leave the study at any time. If you leave the study before it is finished, there will be no penalty to you. You will not lose any benefits to which you may otherwise be entitled. If you choose to tell the researchers why you are leaving the study, your reasons for leaving may be kept as part of the study record. If you decide to leave the study before it is finished, please tell one of the persons listed in Section 10 “Contact Information” (below).

7.2 Could there be any harm to me if I decide to leave the study before it is finished?

No harm is anticipated. If you decide to leave the study before it is finished though, we would like to make sure that you return any unused study drug to us and let us have a final visit with you so that we can ask you about any problems or side affects you may have experienced.

7.3 Could the researchers take me out of the study even if I want to continue to participate?

Yes. There are many reasons why the researchers may need to end your participation in the study. Some examples are:

- ✓ The researcher believes that it is not in your best interest to stay in the study.
- ✓ You become ineligible to participate.
- ✓ Your condition changes and you need treatment that is not allowed while you are taking part in the study.

- ✓ You do not follow instructions from the researchers.
- ✓ The study is suspended or canceled.

8. FINANCIAL INFORMATION

8.1 Who will pay for the costs of the study? Will I or my health plan be billed for any costs of the study?

The study will pay for research-related items or services that are provided only because you are in the study. If you are not sure what these are, see Section 4.1 above or ask the researchers for a list. If you get a bill you think is wrong, call the researchers' number listed in section 10.1.

You or your health plan will pay for all the things you would have paid for even if you were not in the study, like:

- Health care given during the study as part of your regular care. See section 4.1 for a list of tests that are done in the study. The laboratory tests listed in section 4.1 will be paid for by the study when they are collected specifically for the purpose of the study.
- Monitoring for side effects or other problems
- Deductibles or co-pays for these items or services.

If you do not have a health plan, or if you think your health plan may not cover these costs during the study, please talk to the researchers listed in Section 10 below or call your health plan's medical reviewer.

The study team has given you instructions about this research study. It is important that you follow these instructions carefully. If you get sick, have a medical complication, or are injured as a result of your being in the study, call Dr. Rodica Pop-Busui (734-763-3056) or Dr. Lynn Ang (734-232 8058)-immediately. The doctor will either treat you or send you to another doctor for treatment. You will get free medical care at the University of Michigan Health System (UMHS) for any hospitalization or ER visits directly caused by the study drug, device, or procedure. The UMHS and the study doctor are responsible for determining whether your condition was the result of your participation in the study. The UMHS will pay for your treatment only if the need for treatment has been caused by the study drug, device or procedure. This means that you or your health plan must pay for any treatment that is part of your usual medical care, that is related to a medical condition you had before participating in the study, or any illness or injury that occurs during the study that is unrelated to study participation.

By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

8.2 Will I be paid or given anything for taking part in this study?

You will be paid for each in-person visit that you complete. You will be paid $50.00 (each visit) after completing the screening, baseline, and final study visits. In addition, you will be paid $50.00 for each skin sample taken. In the study, up to 4 skin samples will be taken. For all other scheduled in-person visits you will be paid $25.00 after completing the visit. Payment will be by check mailed to the address you provide. The total maximum payment for the study (all visits plus skin samples) will be $450.00. You will only be paid for visits that are completed, and biopsies that are taken.

Beginning July 18th 2017, participants who live more than 75 miles, round trip, from the University of Michigan will be reimbursed for roundtrip mileage at the standard IRS mileage reimbursement rate. The mileage is based on the roundtrip distance between your home address to the study site at Domino's Farms (24 Frank Lloyd Wright Drive, Ann Arbor, MI 48106) or the Kellogg Eye Center (1000 Wall Street, Ann Arbor, MI 48105).

8.3 Who could profit or financially benefit from the study results?

We do not expect anyone involved with the study to profit or financially benefit. If the study is successful, the investigators and the University of Michigan may receive funding for a larger clinical trial of the effects of salsalate

on painful peripheral neuropathy. The Investigators have received funds from the National Institutes of Health to conduct this study.

Research can lead to new discoveries, such as new tests, drugs, or devices. Researchers, their organizations, and other entities, including companies, may potentially benefit from the use of the data or discoveries. You will not have rights to these discoveries or any proceeds from them.

9. CONFIDENTIALITY OF SUBJECT RECORDS AND AUTHORIZATION TO RELEASE YOUR PROTECTED HEALTH INFORMATION

The information below describes how your privacy and the confidentiality of your research records will be protected in this study.

9.1 How will the researchers protect my privacy?

We will keep information collected for the purposes of research in a research file that is separate from your hospital records. Your research file will be identified using a code number, instead of your personal identity. Only the study staff will have access to the research file. Information that is collected that is related to routine care for people with diabetes may be included in your medical record (for example, results of laboratory tests, physical exam findings such as your foot exam), but would not show your research study identification code number.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the sponsor which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law such as child abuse and neglect, or harm to self or others.

The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent document.

9.2 What information about me could be seen by the researchers or by other people? Why? Who might see it?

Signing this form gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study. Information about you may be obtained from any hospital, doctor, and other health care provider involved in your care, including:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)
- Alcohol/substance abuse treatment records
- All records relating to your condition, the treatment you have received, and your response to the treatment

- Billing information
- Your personal identifying information, such as your name and address.

There are many reasons why information about you may be used or seen by the researchers or others during or after this study. Examples include:

- The researchers may need the information to make sure you can take part in the study.
- The researchers may need the information to check your test results or look for side effects.
- University, Food and Drug Administration (FDA), and/or other government officials, auditors, and/or the IRB may need the information to make sure that the study is done in a safe and proper manner.
- Study sponsors or funders, or safety monitors or committees may need the information to:
    - Make sure the study is done safely and properly
    - Learn more about side effects
    - Analyze the results of the study
- Insurance companies or other organizations may need the information in order to pay your medical bills or other costs of your participation in the study.
- The researchers may need to use the information to create a databank of information about your condition or its treatment.
- Information about your study participation may be included in your regular UMHS medical record.
- If you receive any payments for taking part in this study, the University of Michigan accounting department may need your name, address, social security number, payment amount, and related information for tax reporting purposes.
- Federal or State law may require the study team to give information to government agencies. For example, to prevent harm to you or others, or for public health reasons.
- Your study medication will be mailed directly to your home by Belmar Pharmacy. Belmar Pharmacy (Lakewood, CO) has been contracted by the investigator to provide study medications. The study investigators will give Belmar pharmacy your name and mailing address, as well as your study identification code so that they may send the medication to you.

The results of this study could be published in an article, but would not include any information that would let others know who you are.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

9.3 What happens to information about me after the study is over or if I cancel my permission?

As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission or the study is over.

Examples of reasons for this include:

- To avoid losing study results that have already included your information
- To provide limited information for research, education, or other activities (This information would not include your name, social security number, or anything else that could let others know who you are.)
- To help University and government officials make sure that the study was conducted properly

As long as your information is kept within the University of Michigan Health System, it is protected by the Health System's privacy policies. For more information about these policies, ask for a copy of the University of Michigan "Notice of Privacy Practices". This information is also available on the web at http://www.uofmhealth.org/patient+and+visitor+guide/hipaa. Note that once your information has been shared with others as described under Question 9.2, it may no longer be protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

We would also like your permission to keep some of your skin samples, blood and urine samples and medical information, so that we may study it in future research. The future research may be similar to this study or may be completely different.

You can take part in this study even if you decide not to let us keep your skin samples, blood and urine samples, and medical information for future research.

If you give us your permission, we will use your skin, blood, urine samples and medical information for future research. Even if you give us permission now to keep these, you can change your mind later and ask us to destroy it. Keep in mind, however, that once we have analyzed your samples and information we may not be able to take the information out of our research.

We may share your skin, blood, urine samples and medical information with other researchers, so that they can use it in their research. Their research may be similar to this study or may be completely different. Once we have shared your samples and medical information with other researchers, we will not be able to get it back.

You will not find out the results of future research on your skin, blood, urine samples and medical information. Allowing us to do future research on your samples and medical information will not benefit you directly. Information shared with other researchers will not use any personal identifiers that could link the samples and information to you.

Please initial below as to whether you consent to storage and future use of your skin, blood, urine samples and medical information.

_____ Yes, my skin, blood, urine samples and medical information collected in this study may be stored for future use.

_____ No, my blood, urine and skin samples may NOT be stored for future use.

9.4 When does my permission expire?

Your permission does not expire unless you cancel it. You may cancel your permission at any time by writing to the researchers listed in Section 10 "Contact Information" (below).

10. CONTACT INFORMATION

10.1 Who can I contact about this study?

Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Talk about study-related costs to you or your health plan
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator: Rodica Pop-Busui, MD, PhD
Mailing Address: Brehm Tower, Room 5329

	1000 Wall Street Ann Arbor, MI 48105
Telephone:	734-763-3056
Study Coordinator:	Aimee Katona, BS
Mailing Address:	Department of Internal Medicine – MEND 24 Frank Lloyd Wright Drive Lobby G, Suite 1500 Ann Arbor, MI 48105
Telephone:	734-763-0177
Study Coordinator:	Virginia Leone, MA
Mailing Address:	Brehm Tower 1000 Wall Street, Suite 5080 Ann Arbor, MI 48105
Telephone:	734-936-8656
Study Coordinator:	Aaron Burant, BS
Mailing Address:	Brehm Tower 1000 Wall Street, Suite 5080 Ann Arbor, MI 48105
Telephone:	734-615-0552
Study Coordinator:	Cathy Martin, MS, RN, BC-ADM, CDE
Mailing Address:	Brehm Tower 1000 Wall Street, Room 6125 Ann Arbor, MI 48105
Telephone:	734-936-6465

You may also express a concern about a study by contacting the Institutional Review Board listed below.

University of Michigan Medical School Institutional Review Board (IRBMED)
2800 Plymouth Road
Building 520, Room 3214
Ann Arbor, MI 48109-2800
Telephone: 734-763-4768 (For International Studies: US Country Code: 001)
Fax: 734-763-1234
e-mail: irbmed@umich.edu

If you are concerned about a possible violation of your privacy or concerned about a study you may contact the University of Michigan Health System Compliance Help Line at 1-866-990-0111.

When you call or write about a concern, please provide as much information as possible, including the name of the researcher, the IRBMED number (at the top of this form), and details about the problem. This will help University officials to look into your concern. When reporting a concern, you do not have to give your name unless you want to.

11. RECORD OF INFORMATION PROVIDED

11.1 What documents will be given to me?

Your signature in the next section means that you have received copies of all of the following documents:

- A copy of this signed and dated "Consent to be Part of a Research Study" document. (*Note: In addition to the copy you will receive, copies of this document will be stored in a separate confidential research file and may be entered into your regular University of Michigan medical record.)*

12. SIGNATURES

Consent to Participate in the Research Study

I understand the information printed on this form. I have discussed this study, its risks and potential benefits, and my other choices with _____. My questions so far have been answered. I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 10 (above). I understand that I will receive a copy of this form at the time I sign it and later upon request. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Principal Investigator or Designee

I have provided this participant and/or his/her legally authorized representative(s) with information about this study that I believe to be accurate and complete. The participant and/or his/her legally authorized representative(s) indicated that he or she understands the nature of the study, including risks and benefits of participating.

Legal Name: _____

Title: _____

Signature: _____

Date of Signature (mm/dd/yy): _____