INSTITUTO NACIONAL DE CIENCIAS MEDICAS Y NUTRICION SALVADOR ZUBIRAN

INFORMED CONSENT TO PARTICIPATE IN THE PROJECT:

Effects of the early use of dual therapy of dapagliflozin with metformin on glycemic variability in Mexican patients with type 2 diabetes mellitus. An open randomized clinical study.

Principal investigator: Miguel Ángel Gómez Sámano

Address of the researcher: Vasco de Quiroga 15, Belisario Domínguez Secc 16, 14080 Mexico City, CDMX

Researcher's contact phone number (including one for 24-hour emergencies): 5527614851.

Participating researchers: Miguel Ángel Gómez Sámano, Francisco J Gómez Pérez, Gerardo Gamba Ayala, Daniel Cuevas Ramos, Alberto Sigfrido Benítez Rentería, Alejandra Silva Giordano, Lucía Palacios Báez, Bernardette Rivas Gómez, María Guadalupe López Carrasco, Sandra Rodríguez Carranza, Alejandro Raymundo Miranda Cabañas, Juan José Lara Vera, Valerie Paola Vargas Abonce, Jessica Bahena López, Lorena Rojas Vega, Alejandra Domínguez Sánchez, Horacio Correa Carranza.

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INTRODUCTION

You have been invited to participate in a clinical research study. Your participation in this research study is strictly voluntary, which means that you may or may not choose to be part of the study. This format describes the risks and possible benefits of the study so that you can decide whether or not to participate in this research and make an informed decision. This consent form describes the purpose, procedures, possible benefits and risks of the study. This format explains how your medical information will be used and who can see it. You can get a copy of this format to review it calmly or to ask someone else for advice.

The doctor or study staff will answer any questions you may have about this format or about the study. Read this document carefully and do not hesitate to ask about this information. This format may contain words that you do not understand. Please ask the doctor or study staff to explain words or information that is not clear to you.

Once you read the informed consent form, if you wish to participate, you will be asked to sign the pages of this document. You will be given an original signed copy of your consent form so you can take it home and save it for your records.

At the end of the explanation, you should understand the following points:

I. The justification and the objectives of the investigation.
II. The procedures to be used and their purpose, including the identification of what are experimental procedures.
III. The expected risks or inconveniences.
IV. The benefits that can be observed.
V. Alternative procedures that may be advantageous to you

VI. Guarantee to receive answers to the questions and clarify any doubts about the procedures, risks, benefits and other matters related to the investigation and treatment of the matter.
VII. The freedom you have to withdraw your consent at any time and stop participating in the study, without affecting your attention and treatment at the Institute.
VIII. The assurance that you will not be identified in a particular way and that the confidentiality of information regarding your privacy will be maintained.
IX. The researcher's commitment to provide you with the updated information that can be obtained during the study, although this could affect your willingness to continue with your participation.
X. The availability of medical treatment and compensation to which you are legally entitled, in the event of damage caused directly by the investigation.

You can request more time or take this form home before making a final decision on future days.

INVITATION TO PARTICIPATE AS A SUBJECT OF RESEARCH AND DESCRIPTION OF THE PROJECT

Dear Mr. _____

Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ), through the research group, invites you to participate as a research subject in this study that aims to:

To assess whether there is a difference in the control of glucose levels during different hours of the day by comparing two types of treatment: One using two medications (metformin and dapagliflozin) and another using only metformin.

The total duration of the study is 14 weeks

Their participation in the study will last 14 weeks.

The approximate number of participants will be 88 people, which will be searched exclusively at INCMNSZ, in Mexico City.

You were invited to the study because you have a diagnosis of type 2 diabetes mellitus, that you have not taken any medication for the treatment of this disease, which in the last routine tests that were performed found that the average of your blood sugar levels of the last 3 months it is high (that is, it is outside the desired goals) and is also overweight or obese.

For the proper control of your diabetes, it is necessary that, in addition to following an adequate diet and exercise plan, take some medication to reduce blood sugar levels. Particularly in this study, Metformin, a medicine that acts at the liver, intestine and muscle level, will be used so that your body produces and absorbs less sugar in your blood and responds better to insulin (a hormone that helps you use sugar better in our body) and Dapagliflozin which is a medication that allows you to eliminate excess sugar in your blood through the urine.

Currently it has been seen that it is not enough to lower blood sugar levels to maintain adequate diabetes control and prevent the complications of the disease but it is equally important to prevent

these sugar levels from changing abruptly throughout of the day, that is, that they remain within an adequate range in a constant manner, so that there are no sudden ups and downs. In this protocol, it is desired to assess whether the use of two medications (metformin and dapagliflozin) is better at keeping glucose levels stable than the use of a single medication (metformin). You are equally likely to belong to the group that only takes Metformin or to the group that uses both medications at the same time (that is, 50-50) this depends on the result of a random selection and does not depend on the researchers.

STUDY PROCEDURES

The study lasts 14 weeks, in total 8 visits will be made, in the first two weeks (visit 1 and 2) you will be asked to take Metformin and the dose will be adjusted to the one that best tolerates your body, in case you do not tolerate it , you cannot continue in the study. After those two weeks the random selection of the group to which it will belong will be made and from there, for 12 weeks (visits 3,4,5,6,7 and 8) different blood studies and medical evaluations will be carried out in addition to the treatment with the corresponding medications will be followed.
Each visit will last 2 hours.

On visit 3 and 8 (which we will call baseline and final) the following study will be carried out:

• Monitoring of blood sugar variations:
In this study, a device called iPro ™ 2 that measures approximately 5 centimeters and that has a sensor that records your glucose levels during different times of the day will be placed in your abdomen, you will have it placed for 7 continuous days, then it will be removed and the records obtained will be analyzed. This study can cause a little discomfort when placed on the skin and can cause irritation in the area, however it is temporary and does not represent a risk to your health. As it will be used for 7 days at the beginning of the protocol and one week at the end of the protocol, the device will be placed 14 days in total.

In visits 3, 4, 5, 6, 7 and 8 the following studies will be carried out:

Blood and urine samples.

The amount of blood to be taken at each visit is equivalent to a quarter of a glass of water (50 mL) and fat levels (total cholesterol, HDL, LDL, triglycerides), the functioning of your liver (ALT, AST) and the functioning of your kidneys (creatinine, creatinine clearance, uric acid, albuminuria). These tests will allow you to better evaluate the effect of treatments on your body.

In addition, the effectiveness of medications to control your glucose levels will be determined by two tests that measure the amount of sugar in your blood (glycosylated hemoglobin) and the hormone that regulates sugar (insulin).

There will also be another 2 tests that allow you to assess whether the elevation of glucose in your blood is causing damage to your arteries or veins: One of the tests measures the degree of oxidants (substances that damage cells, accelerating their aging and death) and the other measures substances that indicate if there is inflammation.

In total, blood and urine tests will be taken 4 times, you must go to the sampling with an 8-hour fast.

• Quantification of body fat
A special test will be done to quantify or measure the amount of fat in your body.

Your responsibility as a participant in the study is:

• Go to visits when prompted
• Allow blood sampling
• Take the medications indicated for your treatment
• Notify researchers about any discomfort during the study (called an adverse effect on the medication).
• Do not take any type of herbal product or supplement.
• Do not take any medication that is not prescribed by the doctors in the study or notify them about any other product or medication that you need to take.

RISKS AND DISADVANTAGES

Because this is a research study where medications are being administered, it is considered a grade III risk study (which means that the risk is greater than the minimum possible) even though the medications to be evaluated have already been sold for several years and its efficacy and safety has been proven, since there is a possibility that the medications may not work properly or cause certain discomforts.

The risks of blood sampling are: possibility of slight bleeding or bruising at the puncture site, dizziness or fainting and rarely can the blood vessel from where it is obtained be injured. The personnel that will extract the blood sample is trained for it, which will reduce the risk of complications. Extra blood samples may be taken during the study if the study doctor considers it necessary to monitor your health / safety. A blood sample may need to be obtained more than once.

There is no risk of any kind in obtaining the urine sample.

You may also have discomfort during placement of the equipment to monitor your glucose continuously such as pain at the site where the catheter is placed and the possibility of slight bleeding at the site of the catheter puncture.

No risk or discomfort is expected during the measurement of body fat.

BENEFITS

. When deciding to participate in this research study you will be evaluated in your integral health more frequently compared to the standard treatments that are available at the moment, which gives you an advantage as a patient to be able to keep a better control of your disease.

The additional tests that will be carried out will allow you to have a better control of your sugar levels and also evaluate how other organs of your body such as the liver, kidneys and your blood vessels are functioning.

Medications given during the study will lower your blood sugar levels and are expected to allow you to reach the ideal control goals to prevent or lessen the damage that diabetes can cause you.

EFFECTS OR ADVERSE REACTIONS OF THE MEDICINES TO BE TAKEN DURING THE STUDY:

Like all medicines, dapagliflozin can cause side effects, although not everybody gets them.

Stop taking dapagliflozin and see your doctor immediately if you notice any of these serious side effects:

• Excessive loss of body fluids (dehydration): Occurs infrequently (may affect up to 1 in 100 people). Signs of dehydration: Very dry or sticky mouth, feeling of intense thirst, intense feeling of drowsiness or tiredness, poor or no urine during the day, rapid heartbeat.
• Urinary tract infection: Occurs frequently (may affect up to 1 in 10 people). Signs of a urinary tract infection: Fever and / or chills, itchy sensation when urinating, back or side pain. Although it is not very common, if you see blood in your urine, tell your doctor immediately.
• Fournier gangrene: 12 cases have been reported in a period of 5 years. It is a serious infection of the skin of the genitals or of the area between the genitals and the anus. Signs of Fournier gangrene: Pain, high sensitivity, redness or swelling of the genitals or anus, fever or a general feeling of discomfort. These symptoms can get worse quickly, so it is important to notify the doctor immediately so that treatment is given as soon as possible. If their presence is suspected, broad-spectrum antibiotics and surgical debridement will be administered immediately if necessary.
Excessive decrease in blood sugar levels (Hypoglycemia): Occurs frequently when combined with other medications that lower glucose. Signs of excessive decrease in blood sugar levels: Chills, sweating, feeling of great anxiety, rapid heartbeat, feeling of hunger, headache, vision disturbances, change of mood or feeling of confusion. Your doctor will explain how to treat decreased blood sugar levels and what to do if you suffer from any of the above signs.
• Diabetic ketoacidosis: It is rare in patients with type 2 diabetes (may affect up to 1 in 1,000 people). Signs of diabetic ketoacidosis: having frequent nausea or vomiting, stomach pain, excessive thirst, rapid and deep breathing, confusion, unusual sleepiness and tiredness, sweet smell in your breath, a sweet or metallic taste in your mouth, a different smell in your urine or sweat and rapid weight loss. This can

occur regardless of blood sugar levels. Your doctor must decide if you temporarily or permanently stop taking dapagliflozin.

COMMUNICATION OF ADVERSE EFFECTS

If you experience any type of adverse effect, consult your doctor or nurse, even if they are possible side effects that are not mentioned in this document.

The administration of metformin also has side effects and gastrointestinal discomfort is very common, such as nausea, vomiting, diarrhea, abdominal pain and loss of appetite. However, these discomforts resolve spontaneously in most cases. Alterations in taste may also appear. People treated for a long time with metformin may have a reduction in the absorption of vitamin B12, which results in low blood levels and increased risk of anemia.

The most serious complication, although very rare, is lactic acidosis. It occurs, especially in people who have serious harm. It should be suspected in the presence of some discomforts such as respiratory distress, abdominal pain, muscle cramps, fatigue or fatigue, decrease in body temperature, which can eventually lead to a coma. In the event that the presence of acidosis is suspected, stop taking metformin and seek immediate medical attention.

CONCOMITING MEDICINES

Any medication you take, other than the research study medication, including herbal remedies and other non-traditional remedies, is considered a concomitant medication. The study doctors will review with you the concomitant medications that they may continue to take and those that they will not be able to take for the duration of their participation in the study.

ASPECTS OF CONFIDENTIALITY OF YOUR MEDICAL INFORMATION

Your name will not be used in any of the public reports of the study. The laboratory samples obtained will not contain any personal information and will be coded with a serial number to avoid any possibility of identification. By legal provision, laboratory samples, including blood, are classified as bio-infectious hazardous waste and for this reason during the course of the investigation your sample cannot be returned. It is possible that your laboratory samples, as well as your medical and / or genetic information, may be used for other research projects related to the disease being studied. They may not be used for research studies that are related to conditions other than those studied in this project, and these studies must be submitted for approval by an Ethics Committee.

Your samples may be stored by the researchers until the necessary samples are obtained for further analysis.

The codes that identify your sample will only be available to the regular investigators, who are required by law not to disclose their identity. These codes will be stored in a locked file cabinet. Only researchers will have access to them. The study staff (monitors or auditors) may have access to the information of the participants.

There is a possibility that your privacy may be affected as a result of your participation in the study, if necessary to protect your rights and well-being (for example, if you have suffered an injury and require emergency treatment) or if it is requested by the corresponding authority.

Your confidentiality will be protected as marked by law, assigning codes to your information. The code is an identification number that does not include personal data. No information about your person will be shared with others without your authorization.

If you decide to withdraw from the study, you may request the removal and destruction of your biological material and your information. All data collection sheets will be kept with the same confidentiality measures, and only incumbent researchers will have access to the data that has their name. If you wish, you should contact Miguel Ángel Gómez Sámano and express your decision in writing.

The Research Ethics Committee of INCMNSZ approved the completion of this study. This committee is the one who reviews, approves and supervises human research studies at the Institute. In the future, if we identify information that we consider important for your health, we will consult with the Research Ethics Committee to decide the best way to give this information to you and your doctor. In addition, we ask that you authorize us to contact you, if necessary, to request information that could be relevant for the development of this project.

The scientific data obtained as part of this study could be used in publications or medical presentations. Your name and other personal information will be deleted before using the data.

If you request it, your GP will be informed about your participation in the study.

COMPENSATION

There are no costs for you if you participate in this study and there will be no charges for office visits, exams or procedures associated with the study. You will not be awarded monetary compensation for your participation. The costs of your transportation to attend your visits may not be covered by the institute. In the event that adverse reactions occur to any of the study drugs, they will be taken care of and will not generate additional costs. In case of hospitalization due to a serious event related to the medications under study, there is a medical insurance policy.

PARTICIPATION AND WITHDRAWAL OF THE STUDY:

Remember that your participation is VOLUNTARY. If you decide not to participate, both your usual relationship with INCMNSZ and your right to receive medical care or any service will not be affected. If you decide to participate, you have the freedom to withdraw your consent and interrupt your participation at any time without harming your attention at INCMNSZ. You will be informed in time if new information is obtained that may affect your decision to continue the study.

The study may be terminated prematurely if it presents:
• Allergy due to dapagliflozin
• Severe life-threatening illness
• Pregnancy during the study
• Present acute kidney damage
• That does not tolerate at least 1000 mg / day of metformin.

If you are required to leave the study prematurely, you will be offered the accepted and recommended standard treatment for your disease.

BIOETHIC APPROVAL

Both this informed consent format and the research protocol were reviewed and approved / favorable opinion of them, by the Research Ethics Committees and the Research Committee of the Institute, to safeguard the rights, security and welfare of all patients participating in this research study

IDENTIFICATION OF RESEARCHERS:

In case you suffer damage related to the study, please contact Dr. Miguel Ángel Gómez Sámano at INCMNSZ (phone: 5527614851)
If you have questions about the study, you can contact Dr. Miguel Ángel Gómez Sámano at INCMNSZ (phone: 5527614851).

If you have questions about your rights as a participant in the study, you can speak with the president of the Research Ethics Committee of INCMNSZ ([Arturo Galindo Fraga, telephone: 54870900 ext. 6101)

ACTIONS TO FOLLOW AFTER THE TERM OF THE STUDY:

You can request the results of your clinical exams and the conclusions of the study from Dr. Miguel Ángel Gómez Sámano of INCMNSZ (tel. 5527614851). Research is a long and complex process. Obtaining the final results of the project can take several months.

DECLARATION OF INFORMED CONSENT

I have carefully read this informed consent, I have asked all the questions I have had and all have been answered satisfactorily. In order to participate in the study, I agree with all the following points:

• I agree to participate in the study described above. The general objectives, particular to recruitment and possible damages and inconveniences have been explained to my satisfaction.
• I agree to voluntarily donate my biological samples (blood and urine samples) to be used in this study. Likewise, my medical and biological information may be used for the same purposes.
• I agree, if necessary, to be contacted in the future if the project requires collecting additional information or if they find information relevant to my health.

My signature also indicates that I have received a duplicate of this informed consent.

Please answer the following questions:	**YES**	**NO**
Have you read and understood the informed consent form, in your mother tongue?	☐	☐
Have you had the opportunity to ask questions and discuss this study?	☐	☐
Have you received satisfactory answers to all your questions?	☐	☐
Have you received enough information about the study and had enough time to make the decision?		
Do you understand that your participation is voluntary and that you are free to suspend your participation in this study at any time without having to justify your decision and without this affecting your medical care or without losing the benefits to which you otherwise have law?	☐	☐
Do you authorize access to your medical records for this research study and for regulatory purposes to Miguel Ángel Gómez Sámano, his representatives, the auditors, regulatory offices of the study, other government health agencies in Mexico and possibly other government agencies of the health in other countries where the drug under study can be considered for approval of its commercialization?	☐	☐
Do you understand the possible risks, some of which are still unknown, of participating in this study?	☐	☐

Do you understand that you may not receive any direct benefit from participating in this study?

Do you understand that you are not giving up any of your legal rights that you are otherwise entitled to as a subject in a research study? ☐ ☐

Do you understand that the doctor participating in the study can withdraw it without your consent, either because you did not follow the study requirements or if the doctor participating in the study considers that your withdrawal is medically in your best interest? ☐ ☐

Do you understand that the study can be suspended by the study sponsor at any time? ☐ ☐

Do you understand that you will receive a signed and dated original of this Consent Form for your personal records? ☐ ☐

Patient statement: I, _____ declare that it is my decision to participate as a subject of clinical research in the study. My participation is voluntary.

I have been informed that I can refuse to participate or terminate my participation at any time during the study without suffering any penalty or loss of benefits. If I suspend my participation, my medical care will not be affected even in future research studies. I may request additional information about the potential risks or benefits arising from my participation in this study. I can also get the results of my clinical exams if I request them.
If I have questions about the study, I can contact Dr. Miguel Ángel Gómez Sámano tel. 5527614851

I should inform researchers of any changes in my health status (for example, use of new medications, changes in tobacco use) or in the city where I reside, as soon as possible.

I have read and understood all the information they have given me about my participation in the study. I have had the opportunity to discuss it and ask questions. All questions have been answered to my satisfaction. I understand that I will receive a signed copy of this informed consent.

I am clear that if I have questions about my rights as a subject of clinical research in this study, problems, concerns or doubts, and I wish to obtain additional information, or comment on the development of the study, I am free to speak with the Chairman of the Research Ethics Committee of INCMNSZ ([Arturo Galindo Fraga, telephone: 54870900 ext. 6101)

_____ _____

Name of Participant Signature of Participant

_____

Date

_____

Place the participant's fingerprint on this line if you cannot write

_____ _____

Name of legal representative (if applicable) Signature of legal representative

_____

Date

_____ _____

Researcher's Name who explained the document Researcher's Signature

_____

Date

_____ _____

Witness Name 1 Witness Signature 1

_____ _____

Date Relationship with the participant:

Address:_____

_____

_____ _____

Witness Name 2 Witness Signature 2

_____ _____

Date Relationship with the participant:

Address: _____

_____

Place and date: _____

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