Informed Consent Form

Title: Safety, tolerability, and feasibility of empagliflozin therapy in dialysis-dependent ESKD

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Consent and Authorization Document

Research Study Title: Safety, tolerability, and feasibility of empagliflozin therapy in dialysis-dependent ESKD (EMPA-ESKD Study)

Sponsor: This research is being funded by the National Institute of Diabetes and Digestive and Kidney diseases (NIDDK)

STUDY SUMMARY

We have summarized the key information about this research study at the beginning of this consent document. More complete details are included following this summary.

We invite you to take part in a research study because you have end-stage kidney disease (ESKD) and require maintenance hemodialysis three times a week. The decision to participate in the research study is entirely your choice. Your decision regarding study participation will not have any impact on your regular dialysis care.

The purpose of this study is to find out if empagliflozin, a new diabetic medication that has been shown to be very effective in lowering the risk of heart failure, is safe and tolerated in dialysis patients. In the recent years, empagliflozin has become a major tool to prevent heart failure hospitalization and to reduce the risk for cardiovascular death in diabetic and non-diabetic patients. Although patients with severe chronic kidney disease and ESKD have very high risk of heart failure and cardiovascular death, they have been excluded from all of the previous studies. If this medication is found to be well tolerated and safe in dialysis patients through this study, future clinical studies can evaluate if this medication can also reduce the risk of heart failure and cardiovascular death in dialysis patients.

You will be assigned to a treatment group that uses a placebo, 10-mg, or 25-mg dose of empagliflozin. What group you will be in is decided by chance, like flipping a coin. Because this is a blinded study, the study doctor, the study nurse, and you will not know which group to which you are assigned. You will take the study medication for 12 weeks. Your last study visit will be 2 weeks after your last dose of the study medication. All study visits will take place during your regular dialysis sessions. During the study, a study coordinator will frequently follow up with you to see if you have any problems with the study medications. We will be drawing blood samples for safety assessment as well as for future research studies. Some of you will be asked to participate in an additional evaluation of how the drug is handled by people on dialysis. The procedures will be described in more detail later in this document.

You will also be asked if you would like to participate in a related but a separate sub-study (led by Drs. Bunsawat and DiBella) to understand the effect of empagliflozin on your blood vessel and heart function. If you are interested in learning more about this separate study, you can request more information at the end of this consent document.

There are some potential risks of the study medications. There is a risk of loss of confidentiality. There is also a risk associated with blood draw. All the risks will be described in more detail later

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in this document. You may benefit from being in the study, but there is no guarantee of benefits. You might help others in the future by being in this research study.

You will get standard care for your dialysis regardless of your decision to be in this study or not.

You may take this document home to read or to discuss with your family members or doctor before deciding to take part in this research study. Please take your time and read this information carefully. You should ask the research staff if you have any questions about this study, or if there is anything you do not understand. If you decide to take part in the study, you will be asked to sign this form.

BACKGROUND AND PURPOSE

Patients on dialysis have a very high risk of heart failure and heart-related death compared to people who do not require dialysis. While treatment options for heart failure have improved over the years for those without kidney disease, there has been very limited discoveries to improve survival for dialysis patients.

Empagliflozin, a new diabetic medication that works by making the kidney put out more sugar in the urine, has recently shown to have significant efficacy to protect the kidney and to reduce heart failure hospitalization and cardiovascular death in both diabetic and non-diabetic patients. Studies suggest that this medication may have benefits on the heart, fat cells, blood vessels, and possibly other organ systems. The benefit remains consistent whether you have diabetes or not. Empagliflozin is now approved by the U.S. Food and Drug Administration (FDA) to treat not only diabetes but also chronic kidney disease and to reduce the risk of cardiovascular death and hospitalization for heart failure in adults regardless of the diabetes status.

The clinical studies, however, have excluded those with severe kidney disease and those requiring dialysis. The safety of empagliflozin in the dialysis patients has not been established, and thus it is not available for people with end-stage kidney disease. If empagliflozin is safe in dialysis patients, it may potentially become a very powerful tool to lower the risk of heart-related complications and prolong survival.

Although empagliflozin is approved by the FDA to treat patients with chronic kidney disease, heart failure, and/or diabetes, our study will evaluate empagliflozin as an investigational drug to assess if it is safe in patients receiving chronic dialysis. If we can establish safety, the next step would be to conduct a larger clinical study to evaluate its ability to lower heart failure and death risk in dialysis patients.

STUDY PROCEDURES

All study-related visits will occur during your regular dialysis sessions. You will first meet with the study nurse who will explain and describe the study. You many ask as many questions as you like. If you decide to be in this research study, you will be asked to sign this form. We will also ask general information about you such as medical and medication history. Your height, weight, and blood pressure will be measured. About two and half tablespoons of blood will be

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taken from a vein in your arm through your dialysis access to test for safety-related measures. You will not have a separate needle stick for the blood draw.

You will be assigned either to placebo treatment group or one of the two doses of empagliflozin, 10-mg or 25-mg. The treatment you get will be chosen by chance, like flipping a coin. Because this is a blinded study, neither you nor the study doctor will know what treatment you get. You will have about a third chance of being given each treatment. The pills will look alike, so you won't be able to tell placebo from empagliflozin.

Once you start taking the assigned study medication, the study nurse will come see you once a week for the first 4 weeks during one of your dialysis sessions to see how you are doing. At each visit you will be asked to complete a questionnaire to determine if you are tolerating the study medication well. You will also have extra blood draw at week 2, 4, 6 and 8 (a total of 2 tablespoons). At week 12, you week complete your study medication and will have extra blood draw (about 2 ½ tablespoons). We will also ask you to bring your pill bottle every 2 weeks for the first month, then every month for 2 additional months. You will stop the study medication at week 12, and your last follow up will be at week 14. The total volume of blood draw for the study is about 7 tablespoons for the 12-week period.

Pharmacokinetic study
For some of you (about a third of the total study participants, in the order of enrollment into the study), we will ask you to participate in an extra study that will analyze how empagliflozin is handled by people on dialysis and if the drug accumulates over time. The purpose of this extra study is to develop better understanding of long-term safety of using this medication in dialysis patients. If you agree to participate in this extra study, you will have extra blood draw once you have had your assigned study medication for 4 weeks. At the beginning of week 5, we will ask you to take the study medication immediately prior to hemodialysis. We will then draw your blood through your dialysis access, starting at the beginning of your dialysis and over the 4-hour dialysis period (9 times, about 3 tablespoons) during your first dialysis session of the week. On your second and third dialysis sessions of the same week, we will draw your blood at the beginning and the end of your dialysis sessions, for a total of 4 additional times (totaling about a little over a tablespoon). For the entire week that you are doing the pharmacokinetic study, we will ask you to hold empagliflozin for the 5 days and restart it on the following day (i.e., Saturday if you get dialyzed on Mondays, Wednesdays, and Fridays). You will also have blood draw to measure the drug level at week 2 and week 12 of the study period (less than a tablespoon) to learn if the drug accumulates in your blood over time. The total volume of blood draw for this pharmacokinetic study over the 12-week study period will be about 5 tablespoons.

RISKS
One previous study in 8 dialysis patients suggested that empagliflozin is likely safe. Because much of the side effects of empagliflozin relate to increased sugar output in the urine, we believe that the risk of taking empagliflozin is likely to be small in dialysis patients who do not make as much urine. The following will describe known side effects of the drug in patients with normal to moderately low kidney function.

<u>Risks of empagliflozin</u>

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Because empagliflozin increases sugar in the urine, it can increase risk of fungal genital infection. This is typically easily treatable with one dose of fluconazole, but it can rarely become a more serious infection. For people who make normal amount of urine, empagliflozin can also increase urine output and cause dehydration and lowering of blood pressure. For those using insulin and/or certain diabetic medications, such as DiaBeta, Glynase, glyburide, Amaryl (glimepiride), or Diabinese (chlorpropamide), there is a chance that your blood sugar may get low. There is a very rare risk of ketoacidosis, which means you have an excessive amount of ketones (a kind of acid) in your blood. It can make you feel quite sick and cause hospitalization. Empagliflozin has not been linked to increased risk of fracture or amputation, though a similar medication called canagliflozin was initially reported to have possible association.

Although empagliflozin has not been associated with any liver injury, we will also be monitoring your liver function through blood test throughout the study period.

In order to minimize the risk, we will adjust your insulin dose or stop some of your diabetes medication if we are concerned that you are at risk for low sugar reaction. If you make good urine, we will also ask you to avoid being dehydrated while taking this medication to reduce the risk of ketoacidosis and low blood pressure.

Risks of blood draw

Because we will only be using your dialysis access for blood collection, you will not have any additional needle stick or increased infection risk. The total volume of blood to be taken for the main study is about 7 table- spoons over a 12-week period, and for those also participating in the pharmacokinetic study will have a total blood draw for about 12 table spoons over the 12-week period. This amount is well below the limit set by the National Institutes of Health. We will be monitoring your blood count monthly and hold blood draws if you become more anemic with hemoglobin count below 7 g/dL.

Risks of Collection of Medical Record Information

There is a minimal risk of breach of confidentiality regarding collection of medical record information. All research information about you will be handled in a confidential (private) manner consistent with other hospital medical records.

BENEFITS

If the study is successful, we may learn that empagliflozin is safe in dialysis patients. That will allow future clinical studies to assess if empagliflozin can reduce the risk of heart failure and death in dialysis patients. There is also a chance that empagliflozin may help your heart, even for the short duration of this study, though we cannot promise any benefit. By participating in this study, you will provide very important information that may help others on dialysis and possibly to improve their health.

ALTERNATIVE PROCEDURES

You have the option not be part of this study. Your decision to participate or not will not affect the routine care you receive at your dialysis unit.

PERSON TO CONTACT

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If you have questions, complaints, or concerns about this study, you can contact the study coordinator or Monique E. Cho, M.D. at (801) 581-8090.

Institutional Review Board: Contact the Institutional Review Board (IRB) if you have questions regarding your rights as a research participant. Also, contact the IRB if you have questions, complaints, or concerns which you do not feel you can discuss with the investigator. The University of Utah IRB may be reached by phone at (801) 581-3655 or by e-mail at irb@hsc.utah.edu.

Research Participant Advocate: You may also contact the Research Participant Advocate (RPA) by phone at (801) 581-3803 or by email at participant.advocate@hsc.utah.edu.

RESEARCH-RELATED INJURY
If you are hurt from being in this study, you can choose to get medical care at the University of Utah. The University of Utah has not set aside any money to pay the costs of this medical care. The University will work with you to try to address any medical costs.

Costs will be charged to you or your insurance company (if you have insurance). If the study has a sponsor , the costs may be charged to them. Costs can also be charged to others who may have responsibility for paying for your medical care.

Since this is a research study, some health insurance plans may not pay for the costs. By signing this consent form you are not giving up your right to pursue legal action against any parties involved with this research.

The University of Utah is a part of the government. If you are hurt in this study and want to sue the University and its employees and students, special laws may apply.

The Governmental Immunity Act of Utah is a law that controls when a person needs to bring a claim against the government and limits the amount of money a person may recover. You can review sections 63G -7-101 to -904 of the Utah Code.

VOLUNTARY PARTICIPATION
Participation in this research study is voluntary. You have the option to not be part of this study. If you do not take part, you will receive the routine treatment usually provided to patients on dialysis. Your decision to participate or not participate will not affect any other part of your care at this hospital. Refusal to take part or stopping participation will not result in any penalty or loss of benefits to which you are entitled. Your decision to take part or not take part will not affect your legal rights, available remedies, or the quality of health care that you will receive at this hospital.

UNFORESEEABLE RISKS
There may be risks from taking part in this study that are not known to the researchers right now. They may find out new risks while the study is going on. If this happens, the research staff will tell you the new information, whether it may affect you, and what, if anything, to expect.

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RIGHT OF INVESTIGATOR TO WITHDRAW
We expect to continue the study until all participants have been enrolled and all of their information has been collected. However, the study may be stopped at any time by the researchers at this institution or by the National Institutes of Health. The researcher may also withdraw you from the study without your approval. One reason this may happen is because the researcher feels it is necessary for your health and safety. Another reason is if the entire study is stopped.

COSTS AND COMPENSATION TO PARTICIPANTS
There will be no cost to you to take part in the research study.

You will receive compensation for your participation in this study, as follows:

- You will receive $100 at the end of the study as a small token of our appreciation of your time and effort.
- If you participate in the pharmacokinetic study, you will receive additional $75 at the end of the study.

Since you will be paid for participating in this study, it is necessary for us to collect your Social Security Number. You will provide this information for a Federal W-9 Form that is filed with our Accounts Payable department. Accounts Payable will have limited access to the study information (e.g., the name of the study) for payment purposes. The amount you receive for taking part in this study will be turned into the Internal Revenue Service (IRS) as taxable income. You can choose not to provide us with your Social Security Number for this form and still participate in this study; however, we will not be able to pay you as outlined in this consent form.

NEW INFORMATION
During the course of the study, we may find new information that could be important to you. This includes information that may cause you to change your mind about being part of the study. We will notify you if any significant new information becomes available which may affect your health, safety, or willingness to continue in this study.

During the study, we may learn something about your health that could help you and your doctors make decisions about your healthcare. If this happens, we will tell you about these results. We will contact you and make arrangements to discuss this with you.

NUMBER OF PARTICIPANTS
We expect to enroll approximately 75 participants at DaVita dialysis clinics affiliated with University of Utah.

AUTHORIZATION FOR USE OF YOUR PROTECTED HEALTH INFORMATION
Signing this document means you allow us, the researchers in this study, and others working with us to use some information about your health for this research study.

This is the information we will use and disclose in our research records:

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- Demographic and identifying information like name, address, telephone number, sex, age, race
- Your medical history, medications, specific information related to your dialysis treatment (i.e., dialysis access, duration of dialysis, dry weight)
- Your weight, blood pressure before and during dialysis
- All laboratory tests that will be done in the study.
- Any medical emergencies or hospitalizations during the study period
- The results of any medical procedures pertinent to your cardiovascular health during the study period

How we will protect and share your information:

- We will do everything we can to keep your information private. All your blood samples to be stored for future research purpose will be labeled with a code without any identifying information. Any sharing of your data with our collaborators outside of this study group will not include any of your identifying information. Study information will be kept in a secured manner and electronic records will be password protected. Study information regarding your laboratory tests for safety assessment (i.e., your glucose level, electrolytes, liver function test, ketones) may be stored with other information in your medical record. Other doctors, nurses, and third parties (like insurance companies) may be able to see this information as part of the regular treatment, payment, and health care operations of the hospital. We may also need to disclose information if required by law.

- In order to conduct this study and make sure it is conducted as described in this form, the research records may be used and reviewed by others who are working with us on this research:

    - Members of the research team and University of Utah Health
    - The University of Utah Institutional Review Board (IRB), which reviews research involving people to make sure the study protects your rights
    - The members of Data Safety Monitoring Board (DSMB), which oversees safety issues of the study.
    - FDA and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

- The results of this research study will be provided to the sponsor, NIDDK. In addition, data from this study will be put in a public data set that will be available to other research investigators. This public data set will not contain any identifying patient data.

- If we share your identifying information with groups outside of *University of Utah Health Sciences Center,* they may not be required to follow the same federal privacy laws that we follow. They may also share your information again with others not described in this form.



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What if I decide to Not Participate after I sign the Consent and Authorization Form?

- You can tell us anytime that you do not want to be in this study and do not want us to use your health information. You can also tell us in writing. If you change your mind, we will not be able to collect new information about you, and you will be withdrawn from the research study. However, we can continue to use information we have already started to use in our research, as needed to maintain the integrity of the research.

This authorization does not have an expiration date.

Consent for Sample Banking

As part of this study, we will store some of your blood for future use. These future tests will try to provide better understanding of the effects of empagliflozin in different cellular functions. Your samples may be used for genome or exome sequencing in future research. The samples will be stored until they are used up, or for as long as deemed useful for research purposes.

The samples will be sent to a sample storage facility within University of Utah, where they will be kept indefinitely and without information identifying you. The samples will only be shared with researchers approved by the University of Utah or National Institutes of Health. An Institutional Review Board must also approve any future research using your samples. However, if the researchers decide that there is no more use for your samples, you agree that they may be discarded.

Your samples will be coded so that your name is not on the samples. The researchers at NIH will not have the code to link your sample back to your name. Only researchers on this study at the University of Utah will have access to your identifiable information. We will keep your name in a separate place so that we can link your sample back to you later if we need to do so.

You do not have to participate in the blood bank to be in the main part of this study. No matter what you decide to do, your decision will not affect your medical care. You can tell us your choice by **initialing** one of the choices below:

_____ Yes _My sample(s) may be saved for future research on patients with end-stage kidney disease.

_____ No_ My sample(s) must be destroyed at the end of this research project.

You can have your samples removed from this tissue bank later. You will need to contact Dr. Monique Cho at 801-581-8090.

If you give permission for your sample(s) to be saved for future research by the University of Utah or its research partners, the Institutional Review Board may review and approve each new project. The Institutional Review Board may require that you be contacted for your permission

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prior to the use of the sample(s) in a new project if it determines new consent is required for your protection.

Samples and information obtained from you in this research may help in the development of a commercial product by the University of Utah or its research partners. There are no plans to provide financial compensation to you should this occur.

Participation in a separate study to understand the effect of empagliflozin on blood vessels and heart:

YES_____ I would like more information, and I give permission to be contacted about the study.
(Please initial)

NO _____ I am not interested any other studies at this time.
(Please initial)

Because the results from future research will not directly affect your health care, we will not share the results from future studies with you.

Please **INITIAL** the appropriate statement to indicate whether or not you give permission for future contact.

YES_____ I give permission to be contacted in the future for research purposes.
(Please initial)

NO _____ I do not give permission to be contacted in the future for research purposes.
(Please initial)

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CONSENT

I confirm that I have read this consent and authorization document and have had the opportunity to ask questions. I will be given a signed copy of the consent and authorization form to keep. **I agree to take part in this research study and authorize you to use and disclose health information about me for this study, as you have explained in this document.**

_____
Participant's Name

_____ _____
Participant's Signature Date

_____
Name of Person Obtaining Authorization and Consent

_____ _____
Signature of Person Obtaining Authorization and Consent Date

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