Start of the clinical trial: Octuber 1, 2018.
Term of the study: January 31, 2019.

Study Identification. HospitalCG 034/18 clinical study

Official Title: Supplementation of thyroid hormone for TSH targets in patients with chronic kidney disease without renal substitution therapy: randomized, double-blind clinical trial at the Guadalajara Civil Hospital.

1. **Study Identification**. **HospitalCG 034/18 clinical study**

Brief Title: Supplementation of Thyroid Hormone for TSH Control in Patients With Chronic Kidney Disease Without TRR. (TSHrenal) .
Acronym: TSH-renal
Official Title: **Supplementation of thyroid hormone for TSH targets in patients with chronic kidney disease without renal substitution therapy: randomized, double-blind clinical trial at the Guadalajara Civil Hospital.**
Study Type: Interventional (clinical trial).

2. Study Status

- Record Verification Date: march 15, 2019
- **Overall Recruitment Status:** Completed: The study has concluded normally; participants are no longer receiving an intervention or being examined (that is, last participant's last visit has occurred)
- **Study Start Date: Octuber** 1, 2018
- **Primary Completion Date:** January 31, 2019
- **Study Completion Date** March 1, 2019.

3.Sponsor/Collaborators

- Sponsor: Hospital Civil de Guadalajara
- Responsible party: Principal investigator: Guillermo Navarro Blackaller (GBLACKALLER)
- Official Title: Resident of nephrology
- Affilitaion: Hospital Civil de Guadalajara
-

4. Oversight

U.S. FDA-regulated Drug: no
U.S. FDA-regulated Device: no
U.S. FDA IND/IDE: no
Human Subjects Review: Board Status: Approved Approval Number: 034/18
Board Name: Ethics Committee 034/18
Board Affiliation: Hospital Civil de Guadalajara
Phone: 3336147748 Ext: 2584
Email: greenavarroblackalle@hotmail.com
Address: Hospital #278
Data Monitoring: no
FDA Regulated Intervention: no

5. Brief Summary:

Study design: Phase II study, randomized, double-blind, unicentric, two-arm, placebo-controlled clinical trial. Methods and participants: Patients with Chronic Kidney Disease G2-G5 with proteinuria without renal replacement therapy, who come to the clinic of renal

health clinic of the Fray Antonio Alcalde civil hospital. As criteria for non-inclusion, need for dialysis, primary hypothyroidism or pre-existing thyroid disease, ischemic heart disease in a period less than 6 months, arrhythmia, pregnancy, use of drugs that interact with synthesis of thyroid hormones, do not accept informed consent, thyroid stimulating hormone (TSH) <2.5 uiml / L or TSH> 10 uiml / L.

6. Detailed Description:

Thyroid disorders, especially elevated TSH levels in patients with CKD, are frequent. As it is an easy medication to acquire and of little cost compared to the other options, levothyroxine would provide benefits already known in patients with CKD and also a proteinuria effect (knowing each other). as a factor of progression of the CKD a health problem worldwide) being a potentially useful treatment and a dose that the risk is minimal. The study consists of 3 phases, the first phase consists of capturing patients from the renal health clinic, having baseline measurement of the variables. Then, the second phase consists of both groups treating them with medication (levothyroxine with a safe dose for the investigator's population with high cardiovascular risk of 0.25mcg so that the patient's weight range between 50-80kg maintains a dosage of 0.3-0.5mcg / kg / day that the thyroid axis is not affected) of fasting levothyroxine (in the case of taking a drug that interacts with absorption changes its use according to the specified hours, see Table 2) or placebo according to the randomization 1: 1 for three months and that have treatment with ACEI or ARA-2 (specifying which and the dose thereof), with follow-up every 4 weeks (Monitoring thyroid function). The third phase consists of a comparison of the variables studied.

The primary objective is to evaluate the effect of the use of levothyroxine on the levels of proteinuria measured on the test strip of the general urine and protein examination in 24-hour urine patients with chronic kidney disease without renal support therapy with proteinuria, who already receive the standard antiproteinuric treatment with an ACE inhibitor or ARA-2 against placebo and the secondary objectives are to evaluate the changes in proteinuria, according to TSH levels in 2.5-9.9 µiml /L, with the levels of T4L in levels 0.8-1.8mcg / ml), analyze improvement in glomerular filtration rate in patients receiving levothyroxine and at the end of the study and evaluate Tolerability and safety of levothyroxine as antiproteinuric treatment in chronic kidney disease without renal support therapy, and as secondary objectives improvement in cholesterol, triglycerides blood pressure. Any adverse event will be recorded in the adverse event reporting forms. (definition of the International Conference on Harmonization [ICH])

- Study Type: Interventional

Actual Enrollment: 32 participants

Allocation: Randomized

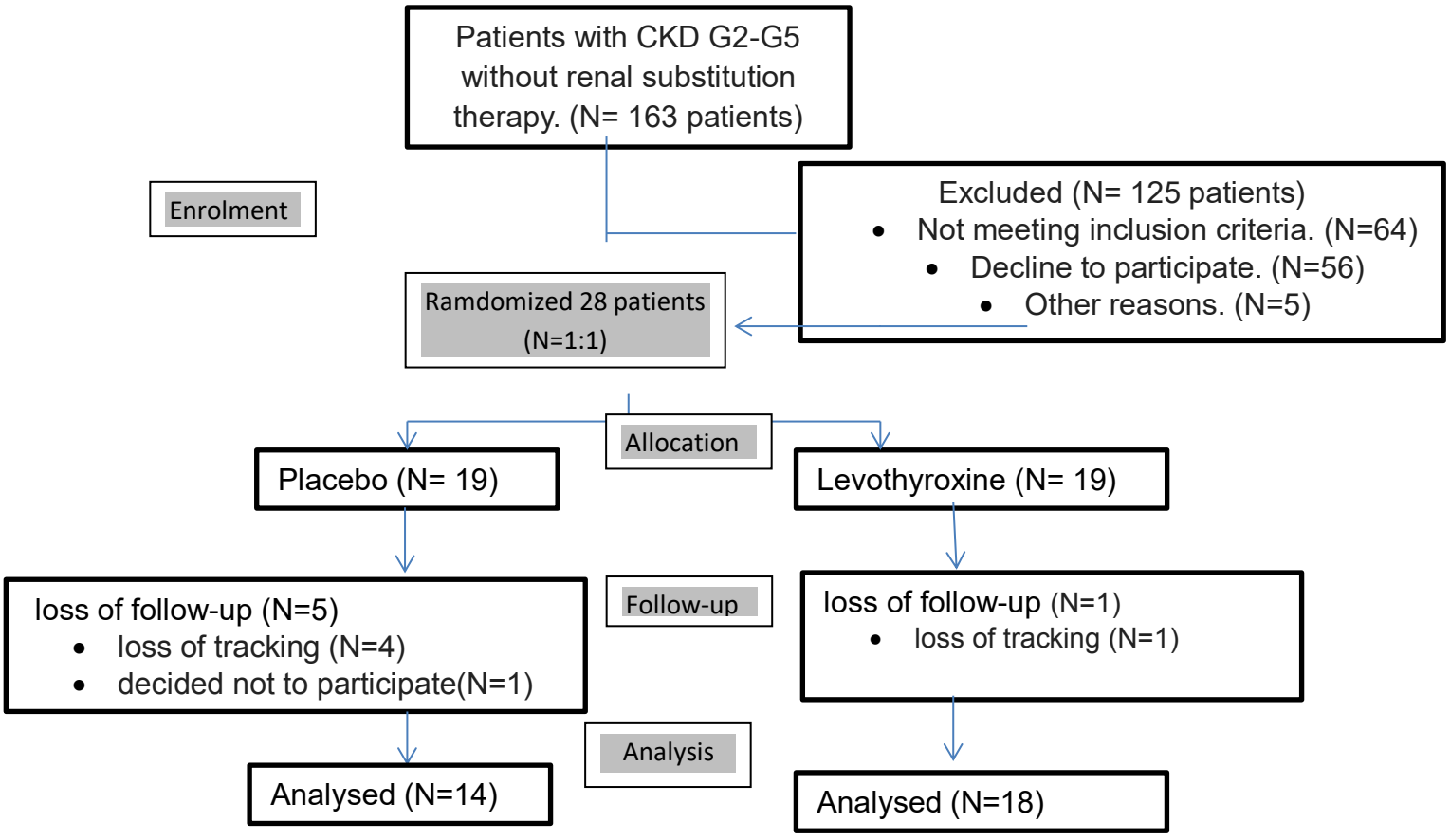
Intervention Model: Parallel Assignment

Phase II study, type placebo controlled clinical trial, randomized of two arms, double blind, unicentric.

Masking: Triple (Participant, Care Provider, Investigator)

The study drug and placebo will be packaged and labeled on the basis of this randomization program, being letters both, for placebo or Levothyroxine, coding that only the third randomization investigator outside the study will know. The letters of the drugs will be preprinted on the study drug labels and will be assigned to double blind treatment as the subjects meet the requirements for the study Both groups treated with fasting medication (levothyroxine) (in the case of taking a drug that interacts with absorption, use of the drug is changed according to the specified hours, see Table 2) or fasting placebo according to the randomization 1: 1 3 months

Participant Flow



Arms and Interventions

Arm	Intervention/treatment
Active Comparator: Group with levothyroxine Patients with Chronic Kidney Disease G2-G5 with proteinuria without renal replacement therapy, who comes to the clinic of renal health clinic of Fray Antonio Alcalde civil hospital. That meet the inclusion criteria. Levothyroxine 25 mcg (1/4 tablet of 100mcg) was administered in fasting the first month, the doctor evaluated with monthly control of TSH levels (if the TSH level was not in the range of TSH 1-2.5 uim / L the second month increase to a dose of 50 mcg (1/2 tablet of 100mcg fasting, or similarly if the patient had a TSH <1 u / L was suspended in medication and it was valued restart the next month the medication if TSH> 2.5u / L) to complete three months of intervention.	Drug: Levothyroxine levothyroxine with a safe dose for our population with high cardiovascular risk of 0.25mcg so that the patient's weight range between 50-80kg maintains a dosage of 0.3-0.5mcg / kg / day that does not affect the thyroid axis) fasting levothyroxine (in the case of taking a drug that interacts with absorption, use of it is changed according to the specified hours, see Table 2), and adjusted according to TSH levels > 1 and normal T4L Other Names: • placebo
Placebo Comparator: Group Placebo atients with Chronic Kidney Disease G2-G5 with proteinuria without renal replacement therapy, who comes to the clinic of renal health clinic of Fray Antonio Alcalde civil hospital. that meet the inclusion criteria. Placebo (1/4 tablet) was administered in fasting the first month, the doctor assessed with monthly control of TSH levels (if the TSH level was not in the range of TSH 1-2.5 UM / L the second month increase at a dose (1/2 tablet fasting, or similarly if the patient had TSH <1 u / L was suspended in medication and it was valued restart the next	Drug: Levothyroxine levothyroxine with a safe dose for our population with high cardiovascular risk of 0.25mcg so that the patient's weight range between 50-80kg maintains a dosage of 0.3-0.5mcg / kg / day that does not affect the thyroid axis) fasting levothyroxine (in the case of taking a drug that interacts with absorption, use of it is changed according to the specified hours, see Table 2), and adjusted according to TSH levels > 1 and normal T4L Other Names: • placebo

month the medication if TSH> 2.5 / month) to complete three months of intervention.	

Eligibility Criteria

Ages Eligible for Study: 18 Years and older

Sexes Eligible for Study: All

Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- • Patients older than 18 years
  - Patients with chronic kidney disease G2-G5 without renal replacement therapy) who attend a renal health clinic.
  - Presence of proteinuria in a test strip, 24 hours urine collection (greater than 150mg / dl in 24hrs urine)
  - TSH <9.9uiml / L and TSH> 2.4 0uiml / L
  - Take an IECA or ARA-2
  - Patients with weight> 50 kg and <80kg
  - Accept informed consent

Exclusion Criteria:

- Chronic dialysis (peritoneal dialysis or hemodialysis)
  - Primary hypothyroidism or preexisting thyroid disease
  - Use of levothyroxine.
  - TSH> 10uiml / L and TSH <2.5 0uiml / L
  - Positive thyroid antibodies
  - Ischemic heart disease in less than 6 months
  - Cardiac arrhythmia
  - Use Medications (Levothyroxine synthesis, see Table 2)
  - Anxiety disorder
  - Pregnancy

- Do not accept consent
- Patients weighing <50 kg and> 80kg

Baseline Measure Information

Table 1. Baseline characteristics of both groups

	Placebo (n= 14 patients)	Levothyroxine (n=18 patients)	P value
Sex (n=% female)	71.42%	55.55%	NA
Age (years)	63.85 DE+/- 15	69.22 DE+/- 8.7	0.41
Diabetes Mellitus (yes or no)	11 (78.57%)	13 (72.22%)	1.00
Hypertension (yes or no)	12 (85.71%)	16 (88.88%)	1.00
Weigth (Kg)	67.90 +/- 13.83	67.01 +/- 11.32	0.88
Obesity (BMI >30 kg/m2)	1 (7.14%)	3 (6.6%)	0.61
ERC G3a (45-59 ml/min/1.73m^2)	0	3 (6.6%)	0.23
ERC G3b (30-44 ml/min/1.73m^2)	2 (14.28%)	4 (22.22%)	0.67
ERC G4 (15-29 ml/min/1.73m^2)	5 (35.71%)	7 (38.88%)	1.00
ERC G5 (<15 ml/min/1.73m^2)	7 (50%)	4 (22.22%)	0.14
eGFR (ml/min/1.73m^2)	9.96 +/- 18.3	13.35 +/- 28	0.16
TSH (uim/L)	4.46 +/- 1.68	5.93 +/- 2.2	0.02®
Protein urine 24/hours (gr/24hrs)	1.28 +/- 1.28	1.71 +/- 1.20	0.14
Cr.s (mg/dl)	3.65 +/- 1.65	2.46 +/- 1.13	0.05®
Albumine (mg/dl)	3.99 +/- 0.41	3.8 +/-0.41	0.24
Tryglicerides (mg/dl)	194 +/- 75.3	144.66 +/- 91.76	0.09
Cholesterol (mg/dl)	170.57 +/- 45.96	165.5 +/- 59.67	0.67
LDL (mg/dl)	75.5 +/- 19	102.38 +/- 31.42	0.01®
Hemoglobin (gr/dl)	11.37 +/- 1.21	11.95 +/- 1.61	0.17
BP systolic (mmHg)	148.14 +/- 27.7	160 +/- 19.4	0.17

BP diastolic (mmHg)	79 +/- 11.72	81.83 +/- 8.2	0.60
IECA o ARA-2 (n=%)	100	100	1.00
Allopurinol (n=%)	100	100	1.00
Statines (n=%)	100	100	1.00

- Study-Specific Measure
- Age*:*
    - Age, Continuous:
    - Age, Categorical:
        - >18 and <80 year
    - Age, Customized: Customizable age categories
- Sex/Gender
    - Sex: Female, Male
- Race and Ethnicity
    - Race and Ethnicity Not Collected (Hispanic race)
- Region of Enrollment: Guadalajara, Mexico

- **Measure Type:** Mean

Measure of Dispersion Standard Deviation

Number of Baseline Participants
38 patients (19 arm Levothyroxine and 19 arm placebo)

Number of Units Analyzed 32 patients (18 arm Levothyroxine and 14 arm placebo)

Analysis Population Type Participants

Measure Analysis Population Description
The sample size was calculated with the population size is 280 patients who attend to Renal Health Clinic, considering that the incidence of subclinical hypothyroidism in grade 3-4 CKD is between 8 to 17,9% a confidence (1-alpha) of 95% = 1.96 and an error rate of 1, the desired population is 50 patients, with 50% distribution, the recommended sample is 13 to 25 patients in each intervention group.

Outcome Measures

Primary Outcome Measure:

1. 24 hours urine Proteinuria in patients with subclinical hypothyroidism and CKD G2-G5 without renal support therapy Randomized clinical trial of levothyroxine group versus placebo [Time Frame: three months]

Outcome Measure Description. Definition: Proteinuria was defined as the presence of proteins in the urine for 24 hours with a range greater than or equal to 0.150 grams / 24 hours. A measurement was made at the beginning and at 3 months of the study to all patients
Measure Type: mean

Measure of Dispersion/Precision: Standard Deviation
Number of Participants Analyzed: 32patientes
Number of Units Analyzed: (18 arm Levothyroxine and 14 arm placebo)
Unit of Measure: grams/ 24 hours

Secondary Outcome Measures:

1. Estimated glomerular filtration rate (eGFR) in patients with subclinical hypothyroidism and CKD G2-G5 without renal support therapy Randomized clinical trial of levothyroxine group versus placebo [Time Frame: three months]

Outcome Measure Description [*] Definition: Outcome Measure Description [*]
Definition: the glomerular filtration rate was calculated based on the seric creatinine expressed in mg / dl, the formula of CKD-EPI was use.

Measure of Dispersion/Precision: Standard Deviation
Number of Participants Analyzed: 32patientes
Number of Units Analyzed: (18 arm Levothyroxine and 14 arm placebo)
Unit of Measure eGFR ml/min/1.73m^2

2. Measurement of lipid profile (cholesterol, LDL and triglycerides) in patients with subclinical hypothyroidism and CKD G2-G5 without renal support therapy Randomized clinical trial of levothyroxine group versus placebo. [Time Frame: three months]

Outcome Measure Description.

Definition: serum cholesterol, triglycerides and LDL cholesterol levels were measured in mg / dl at the beginning and at the end of three months for all patients

Measure of Dispersion/Precision: Standard Deviation

Number of Participants Analyzed: 32patientes
Number of Units Analyzed: (18 arm Levothyroxine and 14 arm placebo)
Unit of Measure mg/dl

Statistical Analyses

- **Type of Statistical Test:** Superiority

Statistical Test of Hypothesis and Method
In the case of quantitative variables, the data are shown as average or median with standard deviation, according to the distribution, be it parametric or non-parametric, respectively.

The nominal variables are shown with frequencies or percentages.

For intergroup and continuous variable comparisons, in the case of qualitative variables, chi2 and, in the case of quantitative variables, the Student's T test or Mann-Whitney U test depending on the distribution of the sample.
The statistical analysis will be carried out with the statistical program SPSS, version 20.

In all cases a value of $p < 0.05$ will be accepted as significant.

Method of Estimation (*or Statistical Test of Hypothesis or Other Statistical Analysis required*)

- Mean Difference (Final Values)
  - Risk Ratio (RR) (Adverse effects)

Parameter Dispersion Type : Standard Deviation

Adverse Event Information
All-Cause Mortality: no death
Eventos adversos graves: no serious adverse event
Other (Not Including Serious) Adverse Events:

During the study the following adverse effects were presented: Urinary tract infection in a single patient of the placebo group (7.14%) and nervousness in two patients of the levothyroxine group (11.11%) (RR 1.55 95% CI (0.15-15.47), value p = 1.0).

None left the study because of the adverse effect. Adverse events were not severe according to the severity scale

Table of non-serious adverse events		
arm Levothyroxine	(N=1) 7.14%	Infections and Infestations (Urinary tract infection)
Arm placebo	(N=2) 11.11%	Psychiatric Disorder (Anxiety)

Duration of urinary tract infection: five days, without complications.

Anxiety duration time: three days, without complications.

Adverse Event Reporting Description

with follow-up every 4 weeks, with thyroid profile control tests and adverse effects will be reported and follow-up. It will be valued in accordance with intensity According to the criteria CTC v. 3.0 (1-5), start date and end thereof, as well as the treatment received.

Overall Limitations and Caveats

Overall Limitations and Caveats At least 12 to 25 patients are needed in each arm. There were missed follow-ups in both arms but more in the placebo arm.

Contacts/Locations

Central Contact Person: Guillermo N Blackaller
Telephone: 013310884749
Email: greenavarroblackalle@hotmail.com

Central Contact Backup: Hospital Civil N Hospital Civil
Telephone: 36124578
Email: greenavarroblackalle@hotmail.com

Study Officials: Jonathan Chavez
Study Director
Hospital Civil de Guadalajara

Locations: **Mexico**

Kidney health clinic, Civil Hospital of Guadalajara

Guadalajara, Jalisco, Mexico, 44280

Contact: Guillermo N Blackaller 3310884749 greenavarroblackalle@hotmail.com

Contact: Guillermo N Blackaller 013310884749 greenavarroblackalle@hotmail.c

Principal Investigator: Guillermo N Blackaller

Table 2 Drugs that interact with levothyroxine
• Drugs that interact with the synthesis of thyroid hormones and / or Levothyroxine: Amiodarone, Lithium and Heparin
Interactions with medications that reduce the absorption of levothyroxine: • Anti-acids (proton pump inhibitors) can inhibit absorption. People should take levothyroxine four to six hours before or after taking these antacids. • Iron supplements: can inhibit absorption. People should take levothyroxine four to six hours before or after taking these • Sucralfate: can inhibit absorption. People should take levothyroxine eight hours before or after taking these • Ciprofloxacin: can inhibit absorption. People should take levothyroxine four to six hours before or after taking these. • Raloxifene: can reduce the absorption of levothyroxine, although evidence to date is not sufficient to establish the scope of the interaction. In one case, the separation of the two drugs in 12 hours appeared to avoid interaction. • Glucocorticoids • Chloroquine • Sevelamer • Orlistat • tyrosine kinase inhibitors
Drugs that potentiate the effect of levothyroxine • Salicylates (medicines used to relieve pain and reduce fever), • dicumarol (medicine to prevent blood clotting), • furosemide in high doses of 250 mg (diuretic medicine), • Clofibrate (medicine to reduce the level of fats in the blood). Effect of levothyroxine on other medications • Decreases the effect of oral hypoglycemic agents up to 5% • Increases warfarin effect

PATIENT INFORMATION LETTER AND INFORMED CONSENT

Name of the Principal Investigator: Guillermo Navarro Blackaller

Associated Researchers: Dr. Jonathan Samuel Chávez Iñiguez

Direction of the Principal Investigator: Civil Hospital of Guadalajara Fray Antonio Alcalde, Nephrology Service. Hospital 278. Colonia Centro. Guadalajara, Jalisco, Mexico. C.P. 44240

What is an informed consent?

You are invited to take part in a clinical research study. Before you can make a decision to participate, you must understand the possible risks and benefits associated with this study. This process is known as informed consent, which means that you:

- Receive detailed information about this research study, including any benefits and risks involved;
- You will be invited to read, sign and date this informed consent, once you understand the study and want to participate. If you do not understand something about the study, or if you have questions, please be sure to request an explanation before you sign this form;
- You will be given a signed and dated copy of this consent.

Your participation in this study is entirely voluntary. You are not obligated to participate in it. Your current medical care will not be affected by your decision to participate or not in this study. If you refuse to participate, this does not imply any penalty or loss of benefits that you enjoy. You must sign this form before any study procedure is performed.

Before you agree to participate in this study, it is very important that you understand the purpose of the study and the type of tests in which you will be invited to participate. The following information will describe the study and its role in the study. You can have a copy of this form to review to your liking and ask for advice from others before signing.

What is the purpose of this study?

The objective of our study is to evaluate the effects of levothyroxine on proteinuria in patients with chronic kidney disease. We propose a randomized clinical trial. Changes in proteins in 24-hour urine, estimated glomerular filtration rate, serum creatinine, cholesterol, blood pressure will be evaluated.

What will I have to do to participate?

To determine if you qualify to enter this study, you will provide a medical history and a thorough physical examination. You will provide a sample of urine, blood (about 2 teaspoons) for 4 weeks 8 weeks and 12 weeks. You will take levothyroxine 25 mcg once a day or a placebo equivalent, for 12 weeks. The visits of the patient after starting the study treatment, will be every 4 weeks, where the samples already specified will be taken, and new medication will be delivered.

What are the risks and discomforts?

In previous studies, levothyroxine at that dose has been well tolerated, and no severe or life-threatening side effects have been reported. Among these side effects, the most frequent are: headache, malaise, tachycardia, diarrhea, anxiety.

When taking blood approximately 10ml (2 tablespoons) for measurements of some studies required in this protocol, there are additional risks, such as discomfort associated with the insertion of the needle into the vein to take blood, infection, which can leave bruises (bruises), Temporary irritation or changes in skin color at the puncture site. Rarely can a person faint by taking blood. You should carefully consider all these risks with one of the doctors participating in the study.

You should call the treating physician immediately if, during the course of this study, any of these side effects (or symptoms) or any other unforeseen side effect develops. If your doctor has told you that your condition aggravated, or that the side effects could be more severe or that new scientific developments could be discovered that indicate that this treatment is not in your best interest, your participation in the study should be suspended.

Are there alternative treatments?

Your alternative is to not participate in this study. Your doctor can provide you with detailed information about your study treatment and the benefits of various treatment options available to you. You have been told that you should feel free to discuss these alternatives (and the prognosis of your illness), as well as other available alternatives, with your doctor. Other options in the treatment of this condition are the use of anti-hypertensive agents from the IECA or ARA 2 family that are already taking, in addition to statins, allopurinol and aldosterone agonist agents.

Will my identity and medical information be kept confidential?
Your identity in this study will be kept confidential and the information obtained about you during the course of this study will remain confidential. By recording the results of the protocol, you will be referred to only by a code number and initials. All the information that refers to your participation in this research will be available to the participants of this work, the Ethics Committee of the Civil Hospital of Guadalajara fray Antonio Alcalde
What are my benefits for participating?
You may not benefit directly from your participation in this study. However, although you may not benefit directly from this research, in the first place there may be a benefit to society, in general, from the knowledge gained in relation to your participation in this protocol. Any information obtained from this research, which may be important to your health or progression of the disease, will be shared with you; we will also have knowledge regarding the improvement in symptoms and clinical signs as well as in the biochemical parameters in the follow-up of patients.
Will I be compensated for participating?
You will not pay for the drug. All costs for the routine treatment of kidney disease or other medical conditions, including any emergency, hospitalization and tests that are not outlined in the study protocol, will be your responsibility. If your disease progresses, you

will be responsible for the cost of any additional diagnostic tests and treatment, as well as the professional fees that result.
You (are) responsible for the cost of any medication (other than urea) that is prescribed for the management of your illness or concomitant diseases, during your participation in this study.

Insurance and Financial Compensation

In case of adverse events adjudged to the drug studied, the Civil Hospital of Guadalajara Fray Antonio Alcalde will NOT pay financial compensation for the treatment of medical complications secondary to the drug or that are part of the natural course of his primary disease, nor will it provide any other compensation of any kind. type to no patient. The medical care you will receive will not change at all, regardless of your original condition as a patient with kidney disease.

What are your rights as a participant in this investigation?
You give your consent voluntarily to participate in this clinical research study. You have been told what your involvement will involve, including possible risks and benefits. Your participation in this research project may be terminated by your doctor without your consent for the following reasons: (1) worsening of your health or other conditions that could be harmful to you if you continue to participate; (2) Failure to keep appointments or taking medication as directed; (3) a serious adverse event reaction (side effect) to the study drug; (4) start of dialysis; (5) the use of medications that have the secondary effect of decreasing the synthesis of thyroid hormones; . You may be withdrawn from participating in the study at any time, at the discretion of the study doctor for any of the reasons you deem appropriate.
You may refuse to participate in this research or withdraw your consent, or also discontinue your participation in this study without penalty and without affecting your future care or your ability to receive alternative medical treatment at any of the Civil Hospitals of the University of Guadalajara. If you withdraw from this protocol you can seek treatment with another doctor of your choice. In the event that you withdraw from the study, the investigator will ask for your permission to continue the follow-up of the case and all the clinical data, which if they are related to the research work will continue to be recorded in your medical record
Declaration of Irrevocable Legal Rights
By your agreement to participate in this study, and by signing this consent form, you do not waive any of your legal rights. You affirm that you have read this consent form. You have been informed that you will receive a copy.
Firms

____ _____
Patient's name (## - Mmm - ####)

____ ____
Name of legal representative (## - Mmm - ####)

Witness Name I (## - Mmm - ####)

_____ _____ _____
Complete address of the witness I Relationship with the patient

Witness Name II ((## - Mmm - ####)

_____ _____ _____
Complete address of the witness II Relationship with the patient

__ _____
Name of Principal Investigator or Signature Date
who interviews and conducts the consent (## Mmm - ####)