INFORMED CONSENT FORM

"Efficacy and safety of bempedoic acid in combination with anti-PCSK9 and ezetimibe in statin-intolerant patients: A randomized crossover trial."

Principal Investigator: Prof. Gennaro Galasso
Participating center: A.O.U. S. Giovanni e Ruggi d'Aragona-Salerno

1. INTRODUCTION

Dear patient, the Investigator has proposed to you participation in a clinical trial. In order to decide whether or not take part in this study, you must receive adequate information such that you understand the risks and benefits associated with it, so that you can provide "informed consent," that is, knowledgeable consent.
Please read this document carefully and take as much time as you need to decide; you may consult a family member or other trusted doctor before deciding. If you have any doubts, you may contact the Investigator. This is a multi-centric study; it means that, several Hospitals and Treatment Centers are involved, in accordance with the Guidelines for Good Clinical Practice (ICH/GCP) and the Declaration of Helsinki for the Protection of Subjects Participating in Clinical Trials.

2. DESCRIPTION OF THE STUDY AND PROCEDURES

This is a phase 4, multicenter, two-way crossover study initiated by the principal Investigator. The study will enroll patients who are intolerant to statins and at high or very high risk of cardiovascular events, who do not achieve adequate LDL cholesterol levels according to their risk class, as recommended by the 2019 ESC/EAS Guidelines for the management of dyslipidemia. Enrolled patients must be statin intolerant and must not have changed their lipid-lowering therapy in the 6 weeks prior to enrollment.
Eligible participants, based on inclusion criteria, will be randomized in a 1:1 allocation ratio, without restrictions, into two treatment sequences of 12 weeks each, respectively, separated by a 4-week washout period.
If you agree to participate, the two treatments in the study will be:

- PCSK9 inhibitors (Evolocumab 140 mg or Alirocumab 75 mg or Alirocumab 150 mg) plus Ezetimibe 10 mg plus bempedoic acid (Treatment A)
- PCSK9 inhibitors (Evolocumab 140 mg or Alirocumab 75 mg or Alirocumab 150 mg) plus Ezetimibe 10 mg (Treatment B)

At the end of the initial 12-week treatment period, each of the two groups will undergo a 4-week medication washout period. This means that for 4 weeks, no patient in the study will receive any therapy. At the end of this period, the two groups will be switched. This means that the group that received triple therapy in the initial phase of the study will be treated for 12 weeks with only the combination therapy of PCSK9 inhibitors and ezetimibe, while the group that received double therapy with PCKS9 inhibitors and ezetimibe will be treated with the triple therapy.
Clinical and laboratory variables will be recorded during the scheduled follow-up visits at weeks 0, 4, 12, 16, 20, and 28. Blood samples will be collected and stored at each visit by the participating centers and analyzed by a central laboratory (A.O.U. San Giovanni di Dio e Ruggi d'Aragona di Salerno). At the end of the study, the decision to continue or discontinue treatment with bempedoic acid, as well as any other therapeutic decision, will be left to the attending physician.

3. STUDY OBJECTIVE

This study is conducted to evaluate the reduction of serum LDL-C levels in patients treated with a combination therapy of PCSK9i + ezetimibe + bempedoic acid compared to those receiving only PCSK9i + ezetimibe combination therapy. In addition to safety and efficacy in reducing LDL-C, the secondary objectives of this study include assessing serum levels of PCSK9, lipid and inflammatory profile, and parameters of glucose metabolism in statin-intolerant patients treated with bempedoic acid, PCSK9 inhibitors, and ezetimibe.
Currently, no previous study has assessed changes in serum levels of PCSK9 in humans during treatment with bempedoic acid, especially in the absence of concomitant statin therapy. This information would enhance current knowledge of the mechanisms of action and could support the hypothesis of a synergistic effect of bempedoic acid and PCSK9 inhibitors.
Furthermore, a recent meta-analysis of five studies involving 3,629 patients has demonstrated that the use of bempedoic acid significantly reduces the risk of new onset or worsening of diabetes. Insulin resistance (IR) is one of the primary mechanisms in the pathophysiology of type 2 diabetes mellitus, hypertension, dyslipidemia, atherosclerotic vascular disease, and has been associated with the risk of coronary artery disease and stroke. No previous study has investigated the effects of bempedoic acid on insulin resistance in humans, especially in patients not treated with statins, which could act as potential confounders. IR, beta-cell sensitivity, and function can be non-invasively measured using homeostasis model assessment (HOMA) calculations based on fasting glucose levels, fasting insulin, and/or C-peptide. The information obtained could provide a clearer picture of the efficacy of this drug in improving glycemic profile in the study population.

4. POPULATION, INVOLVED CENTERS, AND STUDY DURATION

The study will enroll approximately 130 subjects across about 10 clinical centers in Italy. Due to the sample size and the number of participating centers, the evaluation period is estimated to be an average of 6 months. Therefore, data collection and study conclusion are expected to be completed one year after the enrollment begins.
Your eligibility for participation in the study will be verified by the physician, and you will only be enrolled after signing the informed consent form.
If you choose to participate in the study, you will be required to complete all scheduled follow-up visits, including the one at 28 weeks from enrollment.

5. BENEFITS AND RISKS ASSOCIATED WITH PARTICIPATION IN THE STUDY

It cannot be guaranteed with certainty that you will receive benefits from participating in this study. With the use of triple combination therapy, there may be a greater reduction in serum LDL-C levels. The treatments provided in the study, if you choose to participate, will be in accordance with the guidelines for good clinical practice (ICH/GCP).
The knowledge gathered from your participation in this study may benefit others in the future. Your participation contributes to expanding the knowledge base regarding the optimal treatment of patients with your condition and may assist physicians in making treatment decisions for future patients.
The Investigator will discuss with you the risks associated with lipid-lowering drug therapy and will be able to address any questions or concerns you may have regarding the use of these drugs.
In any research study, unforeseen health risks may arise. Every effort will be made to prevent the occurrence of any risk or harm.

6. ALTERNATIVE TREATMENTS

If you choose not to participate in this study, you may decide to undergo traditional care with any other commercially available lipid-lowering therapy, as per standard of care. The Study Physician will discuss with you the risks and benefits of these alternative treatments.

7. CONFIDENTIALITY OF YOUR MEDICAL RECORDS

Your privacy and the confidentiality of your medical records are fundamental. Under the General Data Protection Regulation (GDPR) of the European Union, effective as of May 25, 2018, all personal data collected during participation in the study, including your name, identification numbers, health information, and other data that could personally identify you, will be treated with the utmost confidentiality.
The GDPR also considers patient health information such as weight, height, age, diagnosis, treatment, treatment dates, and similar data as personal data, even if it may be difficult to identify the patient through such information.
If you decide to participate in the study, your medical documentation and personal data will be stored in accordance with European and local data protection laws, ensuring maximum confidentiality and security.
Before being used in this clinical study, your personal data will be encoded using a unique patient number, so that only nurses and treating physicians at your hospital can identify you. When we refer to "personal data" thereafter, we are solely referring to this encoded personal data. Your name, surname, and identification numbers will never be collected as part of this study.
If you decide to participate in the study, your personal data may be processed for the following purposes:

- To analyze and draw conclusions about the study and to create scientific presentations.
- To report adverse events to government health agencies.
- For processing, monitoring, auditing activities, and study control, or for inspections by competent authorities.
- For future reanalysis of study results or for combining your information with information obtained in other studies.
- For the development of new medical products and procedures and other activities related to product development.

By signing this informed consent form, you authorize the Investigator Physician to use anonymized information obtained in the context of this study for scientific communications and publications in medical journals. By "anonymized," it is meant that your name or any other information that could be used to identify you will not be disclosed. With your signature, you also consent to your primary care physician being informed of your participation in this study, unless you have expressly provided contrary instructions.

8. COSTS

You will not receive any compense for participating in the study. You will not be required to pay anything for the standard procedures you will undergo.

9. STUDY PERSONNEL TO CONTACT

For answers to any questions related to this study (such as risks, side effects), or if you believe you have experienced an injury related to the study at any time, you can contact:

Prof. Gennaro Galasso
Phone: 089/673147
Email: ggalasso@unisa.it

10. PARTICIPATION / VOLUNTARY WITHDRAWAL

Participation in the study is entirely voluntary. You may refuse to participate or withdraw from the study at any time without disadvantages or loss of entitlement to benefits. If you wish to withdraw from the study, please contact the Investigator Physician whose name and phone number are provided above.
The Study Physician may terminate your participation at any time if it is believed that continuing your participation in the study could result in significant adverse events. In this case, you will be informed and the reasons will be explained to you.
It may be helpful to inform your family doctor of your participation in the study.

INFORMED CONSENT FORM FOR THE PATIENT

With my signature below, I certify the following:

1. I have understood the information regarding the study, I have been provided with sufficient information about the procedures and devices that will be used in the study, and all my questions have been satisfactorily answered.
2. I freely agree to participate in this study and commit to returning for follow-up visits.
3. I confirm that I have had enough time to evaluate my participation and have received my copy of the information and signature page for informed consent.
4. I understand that my participation in the Study is voluntary, and that my refusal to participate will not affect the medical care I receive. I agree to participate and understand that I may withdraw my consent at any time, before and during the course of the Study, without having to explain the reasons, without any legal consequences, disadvantages, or loss of entitled benefits. If I decide to withdraw or if I need further information at any time, I will discuss it with the Investigator Physician.
5. I consent to adhere to the Study protocols and to provide the Investigator Physician with information about my medical history, medications, or other clinical aspects, and all unexpected events that occur during this Study.
6. I consent to the use of my data for the purposes of the Study. Therefore, I consent to provide direct access to my medical records to representatives of regulatory authorities and other individuals and entities involved in the Study, as outlined in the Information.
7. I consent to inform my family doctor about my participation.

I agree to participate in the Study.

Patient (or legal representative if the patient is unable to consent):

Name and Surname in block letters of the Patient

Signature of the Patient Date Hour

Investigator

I conducted the discussion on informed consent.

Signature of the person obtaining consent Date