Note

on Ethical Approval of the Research Protocol

7 June 2023

By this Note I confirm that the Biomedical Research Ethics Committee of Tbilisi State Medical University has reviewed the Research protocol "The research implementation of the clinical model for evaluation CYP2C19 alleles genotype guided clopidogrel treatment" (Investigator Professor Konstantine Liluashvili) on its #2-2023/103 meeting on 24 May 2023 and gave opinion "Approved with conditions".

The researcher took into consideration all recommendations of the Committee and submitted updated documents.

Considering the updated documents, the Research Ethics Committee of Tbilisi State Medical University gives its positive opinion on the Research Protocol "The research implementation of the clinical model for evaluation CYP2C19 alleles genotype guided clopidogrel treatment" and approves it – the final approval.

Givi Javashvili, MD, PhD
Chairman of TSMU Biomedical Research Ethics Committee
Professor, Head of Family Medicine Department, TSMU
Chairman, National Council on Bioethics

INFORMED CONSENT FORM

Protocol BREC-TSMU#2-2023/103 - "The research implementation of the clinical model for evaluation of CYP2C19 alleles genotype-guided clopidogrel treatment"

JUNE 7, 2023

VISTAMEDI LTD
Ramazi Str. 28, 0159, Tbilisi, Georgia

Consent to participate in the study

Please take part in the study.

This consent form for participation in the study is intended to provide you with comprehensive information. We will explain the research activities' goals, nature and expected results and answer your questions.

Title of the Clinical Study: "The research implementation of the clinical model for evaluation of CYP2C19 allele genotype-guided clopidogrel treatment".

Investigator: _____
(Clinical Study Site)

_____
(First and Last name, Title)

_____ Date: _ _ /_ _ / _ _ _ _
(Signature)

You can freely communicate with the study investigator, ask questions that interest you and are relevant to you, clarify important questions related to the study for you, decide whether you want to participate, and make an informed and independent decision.

You should read the information provided in the informed consent form and think about whether you want to take part in the study.

If you decide to take part in the study, you must confirm your consent by signing this form.

1. Principal Information

Below is some basic information about the study to help you understand the scope of your participation in the study, as well as the main activities and procedures.

Clopidogrel is a drug that is often prescribed for coronary artery disease. The effectiveness of this drug depends on how it is converted into the active substance of the drug in the human body. In turn, the conversion of the drug depends on how active the enzyme system that transforms this drug, *CYP2C19*, is. In different people, this system (*CYP2C19*) is characterized by different activity. There is a laboratory test to determine the activity of this enzyme system - the so-called "clopidogrel resistance" test. In the professional environment, this test is called *CYP2C19 *2, *3* allele genotyping.

The goal of our study is to determine the effectiveness of treatment based on the results of this laboratory analysis, which will support the clinical decision on the choice of clopidogrel or an alternative drug for antiplatelet preventive treatment.

You have undergone percutaneous coronary intervention (PCI) - coronary angiography, coronary artery stenting for ischemic heart disease on _ _ /_ _/_ _ _ _. You are currently receiving appropriate medical treatment and have been given recommendations for the prevention of repeated major adverse cardiovascular events (MACEs).

Based on the results of current studies, you need treatment with clopidogrel or an alternative drug.

To assess your potential resistance to clopidogrel, which may reduce the beneficial effect of this drug, and to allow your doctor to choose an alternative treatment, you should have a laboratory blood test for

clopidogrel resistance. In case of „clopidogrel resistance “, your doctor will select another drug with similar effects.

Laboratory testing for genetic testing of *CYP2C19 *2, *3* alleles will be performed in an accredited diagnostic laboratory with the experience and methodological capabilities to perform this test, using your venous blood sample.

After medication selection, you will continue to receive your routine medical treatment with your usual medications and will be monitored by your physician (healthcare team) and the investigator using the same diagnostic methods that you would receive in real clinical practice, without participation in the study.

At the 3rd, 6th and 12th months of treatment, or when it will be necessary for routine clinical follow-up, or to discontinue treatment with the drug, or change the drug, you will be examined by your doctor (from your medical care team), you will be subjected to a standard clinical diagnostic examination and a survey with special questionnaires.

In addition, the examination results conducted for you during the study period will be collected for the current stage, even if you received outpatient or inpatient medical care at another institution. In such cases, the relevant medical data will be collected for the study follow-up.

During the study, you may be asked to:

- Give a venous blood sample and undergo a “clopidogrel resistance” test (laboratory test for the CYP2C19 *2, *3 allele genotyping);
- Take the treatment prescribed by your doctor;
- At the 3rd, 6th and 12th months of treatment, undergo tests prescribed by your doctor, the results of which are used for routine monitoring of your condition even without participation in the study;
- During the observation period, provide your doctor with information about your health condition, including information about diagnostic and treatment measures taken in other medical institutions;
- Inform us promptly of any decision to stop your participation in the study;
- Permit us to use your medical data for research purposes; Your personal information will not be used in the data processing process and will be protected following applicable laws and research procedures;

The duration of the study is 12 months from start to completion.

The study is being conducted to address important questions that are important for more effective selection of drug therapy for patients with coronary heart disease, reducing health risks and improving quality of life. Thus, the results of this study will be used to achieve significant public benefit.

There are no additional health risks associated with the investigational procedures. In addition to the tests used in everyday medical practice to diagnose and monitor your disease, you will undergo only one laboratory test, the clopidogrel resistance test, which is not hazardous to your health.

The test results do not determine the disease, its severity, prognosis or the side effects of the drugs. It will assess your natural ability to properly absorb the drugs you are taking so that they can have their full effects.

According to current clinical guidelines, clopidogrel or an alternative drug is used without prior examination to treat the diseases for which you are currently being treated.

In addition, you are prescribed other drugs that are also widely used to treat your disease.

During the study, you will not be prescribed any drugs which effects require further study and determination. Therefore, the treatment carried out during the study does not carry any additional risks. The risk to your health is related only to your disease.

The likelihood of developing complications (coronary heart disease) and side effects from medications prescribed for current treatment will remain at the same extent as they would have in real life without participation in the study.

The results of the study will allow us to better understand these approaches to individualization of treatment and risk reduction, as well as to systematically and consistently develop effective measures and extend them to other cases of coronary heart disease, the incidence of which is very high in the population. Thus, by taking part in the study, you will not only benefit your health but also contribute to achieving an important public benefit.

The study may involve risks of breach of confidentiality of your medical and personal data. To avoid this, the procedures for collecting and processing data for research purposes will be protected and carried out by special operations that ensure their security and confidentiality using international standards and best practices. Research activities will be monitored to prevent possible deviations from the research procedures.

Throughout the study, you will be able to make an independent and informed decision regarding your participation in the study. Your participation in the study is voluntary. You can participate or stop participating in the study at any time. However, your doctor (and health care team) will continue to provide clinical diagnostic and treatment measures for achieving the best possible health.

2. Detailed Information

Below, we provide more detailed information about the study activities and procedures in the form of answers to specific questions.

What is the study about?

The study aims to evaluate the results of clopidogrel treatment after coronary artery stenting in patients with coronary artery disease in a setting where this drug is selected based on how well your body can convert the drug into a form that provides the best effect.

To assess in advance how clopidogrel can be metabolized in the body, whether you have resistance to clopidogrel treatment, and to choose clopidogrel or an alternative drug treatment accordingly, we will check your CYP2C19 *2, *3 allele genotype. After selecting and prescribing drugs, we will monitor the course of your disease for 12 months.

What might the researchers ask you to do during the course of the study?

We are asking you to take part in this study. To do this, we will need to randomly assign you in one of the study arms and collect health data throughout the study: at the end of the 3rd, 6th and 12th months.

During this period, you will need to undergo routine medical, laboratory and instrumental examinations. Your disease, coronary artery stenting and drug treatment require these tests for regular follow-up in real clinical practice, a situation in which you would not participate in this study.

You have been pre-selected for inclusion in the study based on your disease and the results of the most recent coronary artery stenting. After receiving your informed consent to participate, we will review your previous clinical investigation results and assess your inclusion criteria for this study. If you have comorbidities, those will be discussed as the study exclusion criteria, you will not participate in the study.

Suppose you decide to take part in the study. In that case, you will be assigned to treatment with clopidogrel or an alternative drug with a similar effect based on the results of the “clopidogrel resistance” test, or you will be assigned to clopidogrel treatment as is currently practiced in real-life clinical practice - without this test. Regardless of your allocation to the study arm, other necessary medications will be selected and prescribed for you in the same way as they would be in real-life clinical practice. You will receive medical treatment that complies with current international and national clinical guidelines.

You will not receive any drug that has not been studied and tested or that is currently being studied and investigated.

We will ask you to give us informed consent to perform a “clopidogrel resistance” test. To do this, we will take a venous blood sample and analyze it in the laboratory. You will not be informed of the test results until study completion, but you will be provided with the laboratory test results after the clinical study completion. You will only be tested once.

If you will be prescribed clopidogrel treatment without having had a “clopidogrel resistance” test, you will not have this test, of course. You will be prescribed clopidogrel in the same way as it is done in real-life clinical practice.

Subsequently, at the end of the 3rd, 6th and 12th months of the study, we will ask you to undergo diagnostic tests necessary for monitoring in everyday clinical practice.

These examinations will include a physician examination, laboratory tests, electrocardiography, echocardiography, and other clinical investigations required for follow-up.

If you undergo any medical examination outside the study or receive any medical care outside the study center at another medical institution, please promptly notify your treating physician and provide medical records reflecting the results of the examinations or medical care. This will not be a reason for withdrawal from the study.

In addition, please allow us to use your health data obtained from this clinical study for research purposes. For this, your data will be collected in a standard medical record and a research data registration form. Research data will be registered separately from your personal identification data (name, surname, address, ID number, address, medical record number) and encrypted to protect against unauthorised access and processing. These procedures will ensure your privacy.

What are the risks and discomforts associated with the study?

Significant health risks and discomfort to your lifestyle associated with the study are not expected.

The diagnostic tests included in the study do not pose any health risks and will not affect the development of complications or worsen your disease/conditions.

The risks to your health are related to your existing disease since coronary heart disease is a chronic disease that cannot be completely cured. In addition, health risks are related to the possibility of complications of this disease.

To some extent, health risks are associated with possible side effects and unwanted consequences of the drugs used for treatment. However, such effects are minimal and will exist even without participation in the study since your drug treatment will still be carried out using drugs with the same effects.

During the study, occasional or repeated non-compliance with the treatment regimen or study procedures may occur and worsen your health. Medical examinations during the observation period will also assess compliance with treatment and study procedures.

There may be other risks associated with the study:

- Emotional risks: The stress and waiting of medical, laboratory and instrumental examination results required by the research procedures may lead to sadness, irritability, anxiety and concern for your health. However, the course of the study and the procedures carried out do not pose a moral risk or harm. Emotional risks may partially contribute to non-compliance with treatment or discontinuation of study participation. Medical assessments during the study will help to detect and avoid such risks.
- Confidentiality risks: These may be associated with a breach of patients' participation confidentiality in research procedures and information about their health status. When developing research procedures, the use of secure methods of collecting, storing, processing and transmitting data is taken into account.
- Financial risks: The "clopidogrel resistance" test will be provided without charge. However, clinical observation will require additional diagnostic measures. The costs of these tests and prescribed medications will not be reimbursed as part of the study. Medical expenses related to hospital care for your disease also will not be reimbursed.
- Employment risks: Participation in the study will not prevent you from finding a job, as it will not limit your ability to work. Such conditions may develop naturally as a result of your illnesses and their complications. The measures provided by the study will not such situations.

What benefits can the research bring?

The research will apply routine diagnostic tests and treatments needed for your condition. They will monitor your health closely for 12 months.

The results of the research will give us a better understanding of a new approach for personalizing and tailoring treatment as well as reducing the risks of diseases and medical interventions, consistently developing effective measures and extending them to other cases of coronary heart disease, the frequency of which is very high in the population. So, by participating in the research, you will also contribute to achieving an important public good.

Are there incentives for participation in the study?

Participation in the study will not be encouraged by monetary or other compensation.

The benefits of research activities may, to some extent, motivate patients to participate in the studies. However, incentives or compensation in the form of financial, material or other benefits are excluded. The diagnostic and therapeutic instruments and services used in the research procedures are readily available and widely used in real-life medical practice.

The study does not consider any social, cultural or ethnic incentives.

The study design ensures men's and women's participation equally.

How will the research data be recorded/registered?

The research activities and procedures you will undergo are components of everyday real-life clinical practice. Therefore, the medical information collected, the results of the examinations and the treatment prescriptions will be recorded and stored in the patient's medical record following the regulations governing medical activity.

The information and data obtained for research purposes will also be recorded in clinical case record forms. They will be used for research purposes. However, these forms will not include any personal information (name, surname, ID number, address, number of medical record) with your medical data. Data in the clinical registration form will be marked with your unique study number, which will be assigned to you upon enrollment in the study. Your permission to use this number will be recorded in a separate list on a separate registration form and stored separately from your medical data.

The clinical case registration forms will not include electrocardiographic, echocardiographic or other images unless they are necessary for diagnostic purposes. As the primary source of medical data, such images will be stored in the patient's medical record in the research center in the established manner.

Your data will be entered into an electronic database and further processed without personal identifiers and under encrypted data variables for research purposes.

This form of recording and registering medical data will prevent the risks of access and processing of your data.

The transfer of research data will be possible only after deidentification and scientific research processing, which will make it impossible to identify them based on personal data.

Of course, medical data will be provided to you or your legal representative upon request in the form and following the rules established in everyday clinical practice.

We cannot transfer your medical information to any of your representatives, including relatives, friends, acquaintances, neighbors or employees who apply to us on your behalf or at your request. The transfer of medical data will be possible only to you and your legal representative authorized in accordance with the legislation of Georgia. Your legal representatives may be:

- Family members (spouse, children, parents, grandparents - from the circle of first-order heirs, in the specified order);
- Relatives (sister, brother - in cases of absence of first-order heirs);
- A person on whose legal support you are, who is your guardian or trustee.

Of course, we will not transfer any information or data forms through unauthorized and unprotected telephone or Internet communication systems, even to you or your legal representative.

For research purposes, your information will be transferred to third parties only after de-identification and scientific research processing in the form (database, scientific and technical report, scientific article), in which it will be impossible to identify your identifiers, including your unique number for participation in the study.

Personal research data in the clinical case registration form and database will be stored for 1 year after the end of the study; after this time, they will be deleted.

Anonymised data will be stored for a longer period, but it will not be possible to identify you using your data through any procedure.

Does research involve data transfer?

Only research data that cannot be identified by personal data may be transferred to the interested research community for scientific research to ensure scientific research standards. Therefore, the data will only be transferred in a form (databases, scientific and technical reports, scientific articles) that does not contain your identifiers, and your unique research participation number will be deleted, thus ensuring your confidentiality.

How will the biological material for the analysis be used?

To perform the “clopidogrel resistance” test required for the study, we will ask you to take one sample of your venous blood, approximately 5 ml. This is the sample that will be analyzed.

The analysis involves extracting your DNA and testing it for the presence of *CYP2C19 *2, *3* alleles. Of course, we will share the results of the analysis with you and, at the same time, use them as data for the assessments required for the study.

The study does not provide studying your entire genome, and we will not provide it. After studying the CYP2C19 *2, *3 alleles, the sample will no longer be stored and will be destroyed following the rules and laboratory procedures.

We asked you to perform several more laboratory tests as part of the study follow-up. These tests can be performed in the laboratory of the study center or another laboratory facility. For these laboratory tests, you may be asked to provide blood and urine samples.

What is the applicability of the final results of the study?

The study for participation in which we are asking you to participate is not a fundamental or real experiment to test a new drug or study the effects of a new drug.

The drugs you are being prescribed have long been used in real-life clinical practice, and their effects are known.

The study is rather applied in nature and aimed at introducing improved approaches to drug selection after a preliminary study and scientific analysis into real-life clinical practice. Such studies are categorized as implementation clinical trials. Information about such studies can be easily found on the Internet.

What decisions can I make about participating in the study?

Participation in the study is voluntary. If you do not decide to participate in the study, this does not mean that you will not continue treatment. In general, you will be able to receive the daily medical care of your choice.

What does early termination of participation in the study entail?

You can terminate participation in the study at any time at your discretion.

The investigator, your doctor, or your treating healthcare team may decide on your early withdrawal from the study. This will be done in the best interests of your health. You will be given a detailed explanation regarding the reasons for your termination of study participation.

Reasons for your early withdrawal from the study may include the development of co-morbid diseases/conditions or complications of an existing disease; the need to use treatment regimens that are not in the best interests of the study; or non-compliance with study procedures or treatment.

Withdrawal from the study does not mean that you will not continue treatment. Generally, you will be able to receive the daily medical care of your choice.

If you have any additional questions, you can ask the investigator or contact the principal investigator who coordinates research activities and procedures and manages the study data: Konstantin Liluashvili, MD, PhD, Associate Professor, Department of General Therapy, TSMU, e-mail: kokalilu@gmail.com, Phone: +995599908899. If you have concerns about your safety as a research subject, please contact the Medical Ethics Council.

3. Consent Statement

I have read the questions set out in the general and detailed information sections of the informed consent form for participation in the study.

I have received information about the aims and objectives of the study, the activities and procedures that will be carried out within the framework of the study, the risks and possible discomfort associated with participation in the study, as well as about records, registration and transfer of data, the use of biological samples for analysis, early withdrawal of the participant from the study and the use of research results.

I have had the opportunity to ask important questions and receive clear answers to all my questions. I voluntarily agree to participate in this study.

I agree to participate in the study and understand that I can stop participating in the study at any time, which will not affect my medical care.

_____ _____

Name of the study participant The study participant's signature

Date of your signature: _ _ /_ _ / _ _ _ _

_____ _____

Name of the study investigator The study investigator's signature

Date of your signature: _ _ /_ _ / _ _ _ _

This part of the document is completed only if the legal representative of the study participant signs the Informed Consent.

I represent the study participant, _____, to whom
(Name, surname)

Participation in the clinical study is offered. As the legal representative of the patient, I was asked to express the patient's interest and confirm his/her participation in the study.

Decision to participate.

I have received information about the goals and objectives of the study, the activities and procedures that will be carried out as part of the study, the risks and possible discomfort associated with participation in the study, as well as about records, registration and transfer of data, the use of biological samples for analysis, early withdrawal of the participant from the study and the use of research results.

I had the opportunity to ask important questions and receive clear answers to all my questions. I voluntarily agree to participate in this study. I had the opportunity to ask questions that were important for the study participants, and I received clear answers.

I, _____, hereby consent
(Name, surname of the legal representative of the study participant)

_____'s participation in the
(Name, surname of the study participant)

Study and understand that he can stop his participation in the study at any time at his discretion without affecting the provision of medical care.

_____ _____

Name of the legal representative of the study participants Legal representative's signature

Date of your signature: _ _ /_ _ / _ _ _ _

_____ _____

Name of the study investigator The study investigator's signature

Date of your signature: _ _ /_ _ / _ _ _ _

This consent form for participation in the study will be stored for 1 year after the end of the study.