INFORMATION AND PERMISSION FORM

Healthy volunteers

TITEL: The effect of obeticholic acid on gut microbiota, gastric motility, accommodation, gastrointestinal peptide in healthy volunteers

EU-nummer: 2020-004180-13

Studie nummer: S64643

Investigators: Hideki Mori (TARGID)

Lieselot Holvoet (TARGID)

Joran Toth (TARGID)

Florencia Carbone(TARGID)

Rina Tanemoto(TARGID)

Emily Ruilova Sosoranga(TARGID)

Alexandra Karpfinger (masterthesis student)

Danaë Dolfeyn (masterthesis student)

Prof. Jeroen Raes (Laboratorium Moleculaire Bacteriologie)

Prof. Dr. Jan Tack (TARGID)

Version No. Date of Publication Description of Changes

Version number	Publication date	Description adjustments
v1.0	08-10-2021	
v2.0	12-11-2021	Updated
v3.0	12-02-2021	Updated
v4.0	30-08-2021	Updated
v5.0	04-10-2021	Updated
v6.0	24-05-2022	Updated
v7.0	06/07/2022	Updated
v8.0	23/11/2022	Updated

Dear Mr and Ms,

This form is intended to inform you about the study for which we request your cooperation. You can then give your written consent to participate on this form. Even after approval, you retain the right to discontinue your participation in the study at any time.
This research was set up by ourselves and is funded by research budgets from our research group. Subject studies are subject to strict international rules and laws. The UZ / KU Leuven Research Ethics Committee supervises compliance with these rules and a number of ethical principles. The Ethics Committee Research UZ / KU Leuven has permitted this study. All actions are carried out by qualified and experienced persons and always by or under the strict supervision of a physician. All your personal data and personal information obtained from this research are covered by medical confidentiality and will only be handled and managed by professional personnel bound by professional secrecy. The GP is informed of the study participation via the clinical workstation. All this is done under the supervision of a doctor who guarantees the confidentiality of this information. If the results of this study are published, presented or discussed outside of our research group, your identity will remain confidential information. If you are referred to, this will only be done on the basis of code numbers. You always have the right to discontinue your participation in the study at any time, also during your participation. You must decide whether or not you wish to participate. Take some time to consider your decision. Please read the following text carefully and go over the questions you still have with the researcher.

Purpose of the study

Functional dyspepsia (FD) is a chronic symptom complex characterized by epigastric pain or burning, bothersome postprandial fullness, or early satiation without a definitive organic cause. Delayed gastric emptying, abnormal acid secretion, visceral hypersensitivity, and psychological stress are thought to be the causes of FD, but they have not been completely elucidated. In recent years, the effect of bile acids on the intestinal environment has attracted attention as a cause of FD. Obeticholic acid has recently been developed as a drug used for liver disease that binds to a bile acid receptor (FXR) and reduces the concentration of bile acids in bile.
The aim of our research protocol is to investigate the effects of changes in bile acid concentration due to obeticholic acid on the intestinal environment, including intestinal bacteria and gastrointestinal hormones, and to elucidate the pathophysiology of FD. In this study, you will take obeticholic acid and placebos for 3 weeks each and investigate changes in gastric motility, gut microbiota, appetite, and gastrointestinal hormone release before and after taking the drug. If this data reveals the effects of bile acids on the intestinal environment, it would be a significant step forward for this type of research.

Conditions so that you can participate.

You can participate in the study if the following conditions are met:

□- Subject is between 18 and 65 years of age.

- Subject has a BMI between 18 and 25 kg/m²

- Subject understands the study procedures and agrees to participate in the study and to comply with the medical regimen by giving written informed consent.

□

You cannot participate in this study if one or more of the following exclusion criteria apply to you:

□- Subject is under the age of legal consent, pregnant or breastfeeding.

- Subject has current symptoms or a history of gastrointestinal or other significant somatic or psychiatric diseases or drug allergies.

- Subject with a BMI ≤ 18 kg/m² or BMI ≥ 25 kg/m².

- Subject has a history of the presence of diabetic or metabolic disease.

- Subject has a significant heart, lung, liver or kidney disease.

- Subject has any history of a neurological disorder.

- Subject has a history of abdominal or other gastrointestinal surgery (including gallbladder removal). Those who have undergone a simple appendectomy more than one year before the screening visit may participate.

- Current use of drugs that can affect gastrointestinal function, motility or sensitivity or gastric acidity and bile acid metabolism.

- Current use of centrally acting medication, including antidepressants, antipsychotics and/or benzodiazepines (in the last year before the screening visit).

□- Current use of warfarin

- Current use of proton pump inhibitors

- High caffeine intake (> 500 ml coffee daily or equivalent).

- Subject consumes excessive alcohol, defined as >14 units per week.

- Subject is currently (defined as within approximately one year of the screening visit) a regular or irregular user (including "recreational use") of any illicit drugs (including marijuana) or has a history of drug (including alcohol) abuse. Further, the subject is unwilling to refrain from the use of drugs during this study.

- Inability or unwillingness to perform all of the study procedures, or the subject is considered unsuitable in any way by the principal investigator.

- Recent participation (<30 days) or simultaneous participation in another clinical study.

Prior participation in a clinical trial of obeticholic acid

There may be other reasons why you cannot participate. The researchers or their employee (s) will go through this with you. If you have any questions regarding the above points, do not hesitate to discuss them with the researchers or their staff.

The course of the study

One of the researchers will provide you with the necessary explanation about the study. If you wish to participate, you will be asked questions about your medical history and medication use, and you will be asked to complete some questionnaires regarding gastrointestinal complaints and your psychological functioning. Researchers will measure your weight, and height. After confirmation of eligibility criteria, researchers will include you as a participant and schedule the study visits in consultation with you.

This study consists of two parts: the duration of obeticholic acid and the duration of the placebo. You will receive both medications in a random order. The treatment interval will be at least four weeks. You will take obeticholic acid (10 mg active ingredient)or placebos every morning for three weeks during each period. You will be blind to the contents of the drug in this study.
Your total visit for exams will be six days. For each study visit, you come sober in the morning to the University Hospital Leuven, Gasthuisberg campus research centre. It means that you have eaten your last meal before 8 pm the night before the examination and will not eat breakfast in the morning.

A gastric motility test will be performed on the days (Visit 1, 3, 5). Before the start of the study, an intravenous catheter will be placed in your arm to collect blood samples. The catheter will be constantly infused with physiological water during the study. A manometry catheter and an aspiration catheter will also be placed through the nose and into the duodenum with a brief fluoroscopic check. After a rest period of 10 minutes, gastrointestinal motility will be measured continuously. The measurement in the fasted state will be performed until a characteristic cycle called a migrating motor complex cycle (MMC) is measured at least once. During migrating motor complex measurement, blood samples will be taken via a syringe that we connect to the line of your catheter every 20 minutes within the first 60 minutes of MMC measurement, then every 10 minutes until the end of MMC phase III. If over 120 min, then blood samples will be collected every 20 min until the end of the MMC measurement (maximum 300 min). During the measurement in the fasted state, you will need to score your appetite feelings every 10 minutes on a scale questionnaire. Duodenal fluids are also aspirated and collected during the fasted state. From 30 minutes after the end of the MMC measurement, you will start to drink a liquid nutrient meal at a constant speed while gastrointestinal motility continues to be monitored. In the

meantime, a blood sample is taken every 10 minutes to measure hormones later. The measurement will finish 60 minutes after the start of the meal. During intragastric pressure measurement, on a scale questionnaire, you will need to score your appetite feelings every 5 minutes. These visits will take about 6-8 hours.

Endoscopies will be performed on the days (Visits 2, 4, 6). Duodenal tissues (maximum 13) are collected using biopsy forceps via an endoscope. An experienced endoscopist will perform all endoscopies. Before the procedure, local anaesthetic xylocaine spray is applied in the throat with no sedation unless demanded by you, in which case intravenous access will be obtained before administration of a sedative. These visits will take about an hour.

Examinations before taking the drug (Visits 1, 2) will be done within seven days before taking placebos or obeticholic acid. Examinations after taking the medication (Visit 3, 4, 5, 6) will be done at least 28 days after taking placebos or obeticholic acid.

For all study visits, you must:

Being sober (no food or drink, with the exception of water and taking necessary medication) from 8 pm, the evening before the examination.

Extra study visits. These short visits are planned to bring stool samples. You will collect stool samples at home using the sampling material before taking medication and after taking tablets on days 2, 4, 7, 14, and 21. You will temporarily store samples in your home freezer. You will deposit stool samples at UZ Leuven (Endoscopy unit) within two weeks after collection. You must make additional visits once between days 7 and 14 during two drug administration periods.

Benefits, risks and taxes

Your participation in this study will not directly benefit you. With this study, we aim to understand the effects of bile acids on the intestinal environment. In this way, we also hope to develop new perspectives on the pathophysiology of functional gastrointestinal disorders. This research has the potential to contribute significantly to the development of new treatments for functional gastrointestinal disorders.

The methods used in this study have previously been used within our research group, and we have found them to be well-tolerated. The applied methods do have a limited burden on the test subjects. Puncturing the blood collection catheter into a forearm vein may cause a momentary and transient painful sensation. Some volunteers will also feel it unpleasant to be inserted the manometry catheter in their nose and tube for the duodenal aspiration. We will use a small amount of radiation to confirm a position of a catheter. The amount of radiation (X-rays) we use is much less than what is said to affect the body. And since we are conducting tests in the necessary place

with the required minimum X-rays dose, there is no need to worry about the effects of radiation. Obeticholic acid is a drug used for liver disease. Since this drug is metabolized in the liver, the amount used for patients with liver disease is usually 5 mg or 10 mg per day, and we will use 10 mg in this study. Taking this medicine during pregnancy and breastfeeding is not confirmed for safety.

Samples

The collected biological samples will be managed and stored in the UZ Leuven biobank under the management of UZ Leuven Herestraat 49 3000 Leuven for two years. The samples will be removed after this period or at least one year after performing the analysis.

What happens to your samples during and after the study?

The traceability of the biological samples is ensured by the client.The administrator of these samples (TARGID, KULeuven) undertakes to use these samples only in the context of this clinical study and to destroy them after the envisaged retention period. The biological material is considered a "gift", and you should be aware that, in principle, you will not receive any financial benefit (royalties) in connection with the development of new therapies resulting from the use of the biological donation you have donated. We will not disclose individual results in this study even to you due to the purely experimental nature of these results and the limited clinical value they provide in the context of current treatment. If you withdraw your consent to participate in the study, you can have your sample (s) destroyed or requested back. Please get in touch with the investigator for this. However, samples already used before your withdrawal of consent cannot destroy retroactively. Data obtained from samples also remain the client's property to guarantee the research's validity.

How many volunteers and patients are participating in this study?

Twelve healthy volunteers will participate in this study. All participants receive both placebos and obeticholic acid.

Cost

Your participation will not incur any costs. You don't need to pay for examinations or doctor's visits for this study.

Fee for participating in the study

You will receive € 950 by bank transfer for your time investment and travel expenses after completing the study.

Drugs

Intercept Pharmaceuticals, Inc. (New York, United States) will provide Obeticholic acid (OCALIVA®) and placebos.

Confidentiality Guarantee

Conducting academic research is one of the legal assignments of UZ Leuven as a client. Your participation in the study means that the researcher collects data about you and that the study's sponsor uses it for research and in the context of scientific and medical publications. Processing your personal data is necessary to realize the scientific research purposes described herein. After all, as a university hospital affiliated with KU Leuven, UZ Leuven must support science and education in the public interest. UZ Leuven would like to clarify the necessity of processing for scientific research performance. As a task in the public interest forms the legal grounds for admission based on which UZ Leuven processes your data in the context of this research. In addition, UZ Leuven is subject to specific legal obligations that may require the processing of your data in the context of security reporting (such as, for example, reporting side effects to supervisory government authorities). Your data will be processed in accordance with the European General Data Protection Regulation (GDPR). UZ Leuven is the controller for your data.

You have the right to ask the investigator what data one has collected about you and what one will use in the context of the study. This information relates to your current clinical situation, your medical history and the results of examinations conducted to treat your health according to the applicable standard of care. You have the right to inspect these data and to have corrections made if they are incorrect.

In certain studies, this right of access can be postponed until after the study has been completed to guarantee the correct course of the study. In that case, this should be explained to the patient.
The investigator is obliged to treat this collected data confidentially.It means that one undertakes never to disclose your name, e.g. in the context of a publication or a conference and that one will encrypt your data (an identification code in the study will replace your identity) before / it passes them on to the database administrator.The investigator and member of one's team will be the only persons who can establish a link between the transferred data and your medical record throughout the clinical trial.

The personal data transferred does not include a combination of elements that allow you to be identified.The research data controller appointed by the client cannot identify you based on the data transferred. This person is responsible for collecting the data collected by all medical

researchers participating in the study and for processing and protecting these data by the Belgian law on the protection of privacy.Your medical file may be viewed by persons bound by professional secrecy, such as representatives of the ethics committees, the study sponsor or an external audit firm to maintain the quality of the study. It will be done only under strict conditions, under the investigator's responsibility for supervision (or one associate's research).
The (coded) study data can be passed on to Belgian or other regulatory authorities, the relevant ethics committees, and other doctors and institutions collaborating with the sponsor.
Your consent to participate in this study means that your medical data will be used for purposes described in this information form and that it will be transferred to the above-mentioned persons and/or institutions. The client will use the collected data in the context of the study in which you participate. If you have any questions about how we use your data, you can always contact your medical researcher. The data protection officer of the research center is also at your disposal.

Contact

If you would like additional information, but also in case of problems or if you have any concerns, you can contact the medical researcher (Prof. Dr. J. Tack) or an employee of his study team (Mori Hideki; email address: hideki.mori@ kuleuven.be) at 016/373765. In case of emergency, you can contact Prof. Dr. J. Tack on the telephone number 016/344225. Outside consultation hours, you must report to the emergency department of your hospital and state that you are participating in a clinical trial. Your record will contain useful information for the treating physician regarding the study.
If you have any questions regarding your rights as a participant in the study, you can contact the ombudsman service in your hospital on the telephone number: 016/344818. If necessary, the ombudsman service can put you in touch with the Ethics Committee.

CONSENT TO PARTICIPATE

The effect of obeticholic acid on gut microbiota, gastric motility, accommodation, and gastrointestinal peptide in healthy volunteers

1. I confirm that I have read the information sheet for the above study and have had an opportunity to ask questions.
2. I have received a copy of this signed and dated informed consent form and the accompanying subject information sheet. I have explained the nature, purpose, duration and predictable effects of the study and what will be expected of the subject. The possible risks and benefits of the study were explained to me. I have been given time and opportunity to ask questions about the research and have received satisfactory answers to all of my questions.
3. I understand that my participation is voluntary and that I am free to withdraw at any time,

without having to justify this decision and without any adverse effect on my further medical treatment.

4. I understand that information about me will be collected during my participation in this study and that the investigator and sponsor ensure the confidentiality of this information following relevant European and Belgian legislation. I understand that the performance of this study by UZ Leuven serves the general interest and that processing my personal data is necessary for conducting this study.

4. I agree to voluntary participation in the above study. I confirm that all information I have provided regarding my medical history is true and correct. I understand that withholding information regarding the exclusion criteria may be detrimental to myself or the study.

5. I agree that all information clinically relevant to me obtained through this study will be communicated to my treating physician.

6. I agree that the sponsor will collect and keep the biological samples described in this document for two years for analysis within the framework of the current study.

Name / signature of volunteer: Date:

_____ _____

I confirm that I have explained the nature, purpose, and foreseeable effects of the study to the person named above.

Name / signature researcher: Date:

_____ _____