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Fondazione IRCCS Ca' Granda
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Head: **Prof. Maurizio Vecchi**

The role of VSL#3® in the treatment of fatigue and other symptoms in Long COVID-19 syndrome: a randomized, double-blind, placebo-controlled study
Study Code: DELong#3/2022

Information Sheet and Informed Consent Form for the adult patient capable of autonomously giving consent

Version No. 1.0 dated 15.05.2022

Dear Sir/Madam,

In the doctor-patient relationship, it is important to have moments of discussion about health choices. In particular, it is your right to receive all the necessary information to make an informed decision.
The purpose of this document is to support the doctor in providing you with accurate and complete information regarding your clinical condition and the treatment in question, so that you can make a free and informed choice.

This document is presented to:

SURNAME: FIRST NAME:
DATE OF BIRTH: PLACE OF BIRTH:
GENDER: M F

by Dr.:
SURNAME: FIRST NAME:
REGISTRATION NUMBER:

Head of Operational Unit

Head of Gastroenterology Unit
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Study Supervisor
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Dear Madam/Sir,

At the IRCCS Ca' Granda Maggiore Policlinico Foundation, hereinafter referred to as the "Institute," you are invited to participate in a study on the effect of a high-concentration probiotic formulation (called VSL#3) in the treatment of fatigue following SARS-CoV-2 infection.

The title of the study is: "The role of VSL#3 in the treatment of fatigue and other symptoms in Long COVID-19 syndrome: a randomized, double-blind, placebo-controlled study."

This study is a national single-center study, which means it is exclusively conducted in this facility. To conduct this study, we need the collaboration and availability of individuals who, like you, meet the scientific requirements for the evaluation that will be performed. Therefore, we invite you to participate in this study, for which you have already received detailed information from the responsible doctor, Prof. Flavio Caprioli.

Before making the decision to accept or refuse participation, we kindly ask you to carefully read these pages, taking all the time you need, and to ask for clarification if you have not understood or need further information. Additionally, if desired, you can seek advice from your family members or a trusted doctor before making a decision.

GENERAL INFORMATION

The general objective of this study is to evaluate the efficacy of VSL#3® compared to placebo in improving the symptom of fatigue in patients with Long COVID-19 syndrome. The placebo is a product that is entirely identical to VSL#3® in terms of taste, color, and packaging but has no biological effect.

In particular, this study aims to obtain data on the benefit of a high-concentration probiotic on the clinical symptoms of patients with Long COVID-19 syndrome following continuous intake.

Ninety-six patients will participate in the study. These patients will be selected among those affected by the same condition as you. If you agree to participate, you will undergo an initial visit to verify

that your conditions meet the criteria required by the study. During this visit, you will meet the doctors responsible for the preliminary evaluation under the supervision of Prof. Caprioli. Once eligibility for the study is declared, you will need to take the product that will be provided to you regularly, following the instructions of the study staff, and attend the required study.

STUDY PROCEDURES

If you decide to participate in the study, the following visits and procedures will be conducted:
Visit 1 (screening visit): During this visit, the eligibility criteria for the study will be verified. The expected duration of this visit will be 20 minutes.
Visit 2 (2 weeks after Visit 1): The estimated duration of this visit is 20 minutes and includes the following procedures:

- Patients will be randomized, and one group will receive the experimental probiotic treatment VSL#3®, while the other group will receive a "placebo," which is a pharmacologically inactive substance. Randomization means that the assignment to one of the aforementioned treatment groups will follow a random statistical criterion that cannot be influenced by the doctor or the subject's condition. This process will be carried out in a "double-blind" manner, meaning neither the patient nor the researching doctor will be aware of the assigned therapy until the research is completed. However, it will be ensured that, if necessary, immediate knowledge of the treatment received will be possible.
- You will be asked to complete a battery of questionnaires aimed at evaluating fatigue, visual quality, anxiety and depression status, and overall health status.
- Approximately 20 ml of blood will be collected, and you will be asked to provide a stool sample preserved in a sterile jar. The collected samples will be sent to the Mucosal Immunology Laboratory of the European Institute of Oncology under the responsibility of Prof. Federica Facciotti for the necessary investigations (intestinal flora composition and measurement of inflammatory parameters in the blood, such as cytokines). At the end of the study, any remaining biological sample will be destroyed and not further preserved.
- You will be provided with the product to be taken in the quantity necessary to cover the 28-day treatment period. You will be instructed to take the product in sachets twice a day for 28 consecutive days.

Visit 3 (after 28 days of treatment): the duration of this visit is approximately 15 minutes, and the procedures are the same as in Visit 2: completion of questionnaires, collection of 20 ml of blood, and delivery of a stool sample for the aforementioned analyses.
Visit 4 (4 weeks after the end of treatment): the duration of this final visit is approximately 15 minutes. During this visit, your clinical condition and the persistence or absence of any effects observed at the end of treatment will be evaluated, even at 4 weeks after the cessation of

administration. Any adverse reactions that occurred during treatment and in the weeks following its discontinuation will also be recorded.
Additionally, you will be informed about the treatment you were assigned to at the end of the study.

EXPECTED BENEFITS OF THE STUDY AND BENEFITS FOR THE PATIENT

The potential benefits of participating in this study are as follows. Currently, there is no available treatment for Long COVID-19 syndrome. The information we obtain through this study will allow us to determine if a high-concentration probiotic treatment is effective in treating this condition. If this hypothesis proves to be true, you may benefit from it if you are enrolled in the treatment group or at the end of the study itself. In fact, participation in the placebo group of the study does not preclude subsequent therapy with VSL#3 after the study is completed.

RISKS/DISCOMFORTS FOR THE PATIENT AND SIDE EFFECTS

Participation in the study may involve some discomforts related to the administration of treatments and/or planned control investigations. Regarding the intake of VSL#3®, the formulation proposed in the study is the same patented product available as a dietary supplement in pharmacies. According to the product's technical specifications, no undesirable effects are reported from the ingestion of the product, except for a possible increase in abdominal bloating in the first few days of taking the probiotic, particularly if the diet is rich in carbohydrates and fats. However, in the event of any issues, we would like to inform you that as part of the trial, you will be under close medical supervision by the researchers who can address and mitigate any problems that may arise. As for the investigations conducted in the study, the risks associated with blood collection are comparable to any other routine blood tests performed by your general practitioner. On the other hand, risks arising from the collection of stool samples, which will be requested to be performed at home, cannot be predicted. If you decide not to participate in this study during the screening visit, blood and stool analyses will not be conducted.

INSURANCE

To cover any damages that may arise from participating in the study, we inform you that our Institute has obtained appropriate insurance coverage in case it is proven that you have suffered harm as a result of your participation in the study. If you experience any injuries during this study, the doctor will discuss the available treatment options with you.

FERTILE AGE, REPRODUCTION, PREGNANCY, AND BREASTFEEDING

If you are a woman of fertile age, you should not initiate a pregnancy during the study period. If a pregnancy does occur, you must immediately inform the responsible doctor.
Similarly, if you are breastfeeding, you should not participate in this study.

PARTICIPATION IN THE RESEARCH

You are free to decline participation in the study. In this case, you will still receive the standard therapies provided for the condition you are affected by, although a standard treatment for Long COVID-19 syndrome has not yet been identified.
Your participation in this study is entirely voluntary, and you can withdraw from the study at any time. If you decide to withdraw, you are not obligated to provide an explanation, but you must promptly inform the study doctor, Prof. Flavio Caprioli. Likewise, the study may be discontinued if the doctor does not observe any benefit or if undesired effects or other factors occur. In such cases, you will be promptly informed about alternative valid treatments for your condition and can discuss them with the doctor. If any data become available that could influence the decision to continue the study, you will be promptly informed.
Participating in the study will not involve any costs on your part.
The study protocol that has been proposed to you has been prepared in accordance with the Good Clinical Practice guidelines of the European Union and the current revision of the Helsinki Declaration. It has been approved by the Ethics Committee of the Milan Area 2.

INFORMATION REGARDING STUDY RESULTS

If you are interested, you can request to be informed about the study results at the end of the study.

CONFIDENTIALITY

To protect the privacy of your personal data, you will be asked to read and sign a separate Privacy Information and Informed Consent form in accordance with Regulation EU 679/2016 and the current national privacy regulations.

Written Consent Declaration for Participation in the Clinical Study
for a capable adult patient to provide personal consent

I, the undersigned .....declare that I have received comprehensive explanations from Dr..... regarding the request to participate in the experimental study mentioned above, as outlined in the attached information sheet, a copy of which has been provided to me well in advance. I confirm that I have been able to discuss the provided information, ask any necessary questions, and received satisfactory answers. I have also had the opportunity to seek further information about the study from a trusted individual. Therefore, I freely accept to participate in the study, understanding the purpose of the request and comprehending the associated risks and benefits. I consent to inform my General Practitioner of my participation in the study. I am aware of my right to withdraw from the study at any time. Furthermore, I have been informed of my right to have unrestricted access to documentation related to the study (insurance, clinical-scientific, and pharmacotherapeutic) and the evaluation expressed by the Ethical Committee.

Patient's Signature:
.....
Date.....
Doctor's Signature (informing the patient):
....
Date.....
Identification Number:

[*If the patient is unable to read or sign, an independent witness, separate from the investigator and sponsor, must be present throughout the entire discussion regarding informed consent. The witness must personally sign and date the informed consent declaration after the form itself and any other written information have been read and explained to the subject, and the subject has expressed verbal consent to participate in the study*].

In this case:

I, the undersigned..... attest that Dr. ..... has thoroughly explained to Mr./Ms. ..... the characteristics of the aforementioned experimental study, as outlined in the attached information sheet, and that the individual, having had the opportunity to ask any necessary questions, has freely agreed to participate in the study.

Signature of independent witness:

…….. Date: ……

Signature of the informing physician:

…….. Date: ……

Identification number: …….