Official title of the trial Effect of oral L-arginine 3.32 g per day on oxidative stress and influence on beta cell function and insulin resistance. A Phase 3, Randomized, Double-Blind, Placebo-Controlled Exploratory Study in Overweight and Obese Patients With Prediabetes

Official title of the trial in terms more understandable for the patient Effect of oral L-arginine (3.32g per day) on oxidative stress (inflammation), beta cell function and insulin resistance.

Structure where the experimentation will take place

In this hospital of ours, IRCCS San Raffaele Hospital, you are offered to participate in a national study that wants to test a new food supplement, on patients suffering from the same condition as you (prediabetes and obesity or overweight) with the aim of monitoring the effectiveness of this treatment compared to the one currently in use

Trial Coordinator Center

_____IRCCS San Raffaele_____ Hospital

Registry in which you have registered or will register the trial (if applicable) and any identification code if available

Identification code _1808_____

Principal investigator at the site *(indicate the Trial Manager)*

Name of Professor Andrea Giustina_____

_____UO Endocrinologia_____ Operating Unit

Sponsor/Promoter DAMOR Farmaceutici _____

Possible funding body DAMOR Farmaceutici

Competent local Ethics Committee

CET Lombardia 1

This document consists of the following sections:

A. PREMISE
B. INFORMATION SECTION. TRIAL SUMMARY: KEY INFORMATION
C. INFORMATION SECTION. FURTHER INSIGHTS
D. CONSENT SECTION

Dear Ms/Sir, the information contained in this information sheet is very detailed. We ask you to agree to participate in the trial ONLY after having carefully read this information sheet and having had a COMPREHENSIVE INTERVIEW with a member of the trial group who will have to dedicate the NECESSARY TIME to fully understand what is proposed to you.

A. PREMISE

Dear Madam/Sir,
We propose that you participate in the clinical trial, which we explain below.

You have the right to be informed about the purpose and characteristics of the trial so that you can make an informed and free decision about whether to participate.

The purpose of this document is to inform you about the nature of the trial, the purpose it is intended for, what participation will mean for you, including your rights and responsibilities.

Please read the following carefully. The researchers involved in this project, some of whom are listed at the beginning of this document, are available to answer your questions. No question that comes to mind is trivial: don't be afraid to ask it!

In addition to us, you can discuss the proposal contained in this document with your family doctor, your family members and other trusted persons. Take all the time you need to decide. You can take home an unsigned copy of this document to think about it or to discuss it with others before making a decision.

If you decide not to participate in the trial, you will still receive the best possible care for patients with your condition/disease. Its refusal will in no way be interpreted as a lack of trust.

Once you have read all this information note, have received answers to any questions you may have asked and have decided to participate in the trial, you will be asked to sign a consent form, of which you will receive a paper copy.

If he or she is unable to sign the informed consent, the procedure for discussion and participation in the research will take place in the presence of an impartial witness and may also be documented and recorded using appropriate alternative means, such as audio or video recordings. At the conclusion of all this, the impartial witness will sign the consent form.

The Principal Investigator

B. INFORMATION SECTION.
GENERAL SUMMARY OF THE TRIAL: KEY INFORMATION

This section aims to present in a synthetic way the key aspects of the experimentation to which we propose to join. The following sections will provide more details in order to give you the opportunity to give or not a fully informed consent to your participation in the trial.

- Why am I being asked to participate in this trial?

You have been included among those who are being asked to participate in this trial because you have certain clinical features that will be better specified later in section C of this information document.

- What are the objectives of the trial? How many centers and patients will take part?

With the research that we present here, we intend to obtain data to answer this question "Is it possible to reduce oxidative stress and therefore improve beta cell function and reduce insulin resistance in overweight/obese patients with prediabetes by taking L-Arginine supplementation? We are conducting this experiment to understand if the new approach is better, the same or worse than the usual one. The usual approach is to propose the low-calorie diet and physical exercise to the patient in order to achieve weight loss and consequently an improvement in metabolic indices."

The trial is scheduled to take place in a center in a country and include a total of 42 patients, including 42 patients at our center.

- What is the routine care approach for the treatment of the disease

Prediabetes in overweight or obese patients is usually treated by subjecting the patient to a low-calorie diet combined with exercise. Patients who will be enrolled in the control group will receive a low-calorie Mediterranean diet and will have to follow a physical activity program.

- Is it my free choice to decide whether or not to participate?

You can freely choose whether or not to participate in the trial. Even after accepting, you can change your mind at any time. In this case, however, you will receive the standard therapies provided for your disease, which are those just indicated above, which however also have potential risks and benefits.

- If I decide not to give my consent to participate in the trial, what choices do I have?

In the event that you decide not to join the trial, you can still be followed by the clinical center that is treating you and will be treated using the best approved (non-experimental) therapeutic methodologies for your disease. In addition, he will be able to participate in another trial that may be underway.

- What happens if I decide to participate in the trial?

If you decide to participate in the trial, you will be treated with either the supplement L-bioarginine or placebo for 90 days (you will be randomly associated with one of these two groups with a 1:1 ratio). Once treatment is complete, he will be followed up at follow-up visit from day 91 to day 95. The entire participation will reach a total of 95 days.

The entire programme of visits and examinations planned during the trial is reported in the next section: section C, point 3 "What examinations, tests and procedures are included in the trial?".

- What are the risks and benefits if I participate in the trial?

Both risks and benefits can arise from participation in this trial. It is important to evaluate them carefully before making a decision.

Expected benefits

The following benefits are to be expected from participation in this study*:*

By joining the trial, it will have the opportunity to be treated with a molecule that could play an active role in reducing oxidative stress (inflammation) and delaying the development of type 2 diabetes in patients with pre-diabetes. Several studies have shown that supplementation with L-Arginine has beneficial effects on the reduction of oxidative stress and endothelial function, insulin resistance and beta cell function. L-Arginine is a semi-essential amino acid, and plays a fundamental role in protecting endothelial and cardiac function, insulin secretion and insulin sensitivity. Many preclinical and clinical studies have demonstrated benefits of supplementation of this molecule in insulin-resistant, prediabetic and diabetic patients. Specifically, it has a protective role on the functionality of beta cells and improves insulin sensitivity, reduces oxidative stress, improves endothelial function and reduces the share of white adipose tissue in favor of brown adipose tissue.

Potential risks

We want to make sure that you understand some of the possible risks early on: additional information can be found in the next section "What risks may I face if I participate in this trial"?

Previous studies have reported no side effects related to the administration of L-Arginine.

- Is the consent final? Can I decide to withdraw from the clinical trial (voluntary exit)?

You can decide to withdraw from the trial at any time and for any reason, without having to justify your decision.

If you decide not to participate anymore, let one of the investigators know as soon as possible: it is important to stop the treatment safely. Your doctor may consider a final check-up/examination appropriate.

Your doctor will keep you informed of any changes in the trial that may affect your willingness to participate.

- Are there any reasons why the trial could be interrupted not by my will (early termination)?

Yes, the investigator may decide to stop his participation in the trial if:

- His health conditions change and participating in the trial is potentially harmful
- New information became available and experimentation was no longer in its best interest
- You do not follow the agreed rules for participation in the trial
- For women: if you happen to become pregnant during the trial
- The trial was interrupted by the competent authorities or by the Promoter.

In the event of a study interruption, the patient will still have the opportunity to continue the planned follow-up visits in the event of withdrawal of consent, suspension of the trial,

- Will I be able to access the results of the trial?
The investigators and the sponsor undertake to make the results of the study available to the scientific community. You may ask the investigator to inform you of the general results of the trial.

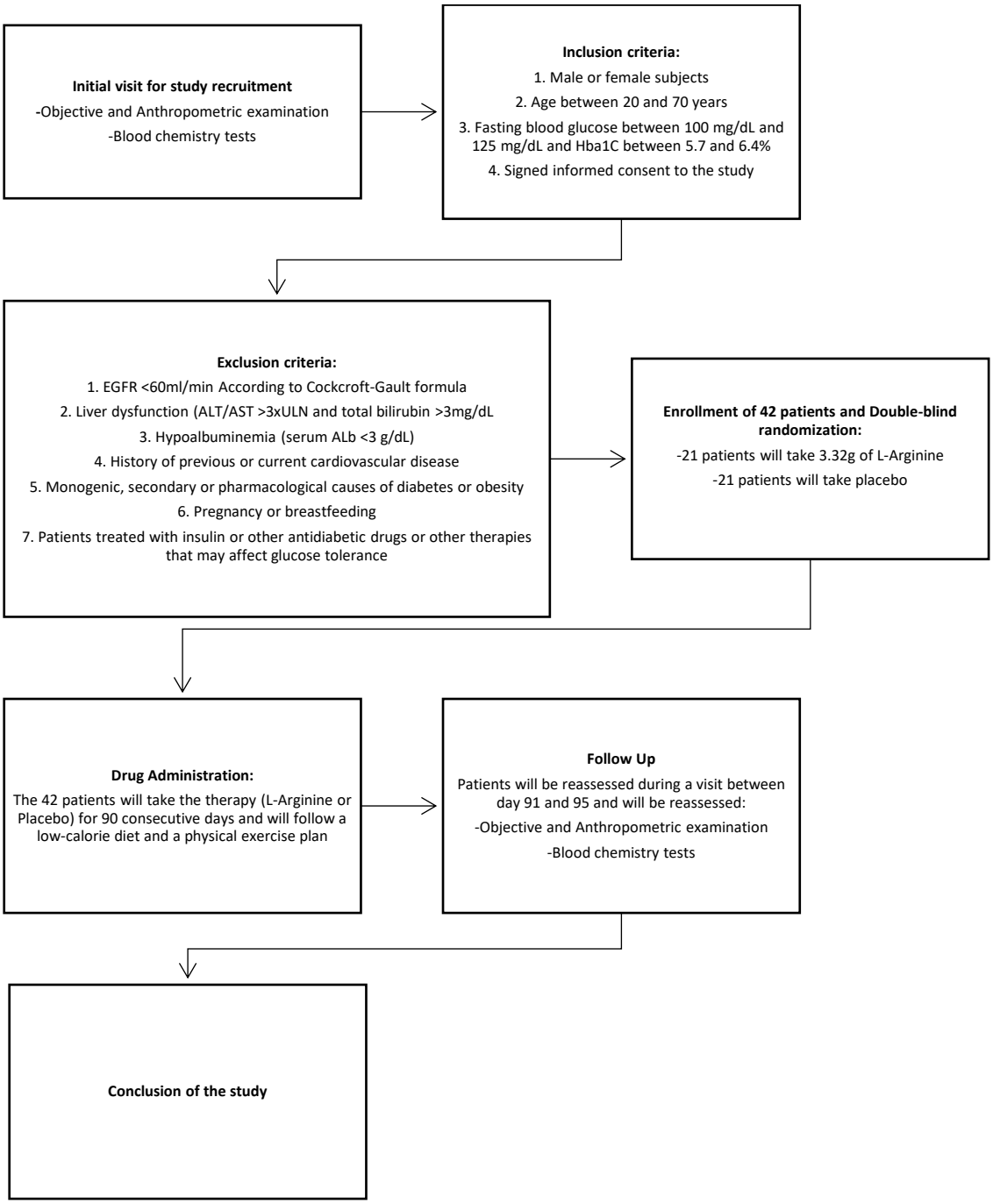
C. INFORMATION SECTION. FURTHER INSIGHTS

1. What is the purpose of the trial?

This study is a phase 2, randomized, double-blind, placebo-controlled study in overweight and obese patients with pre-diabetes. The study involves 42 obese or overweight patients with pre-diabetes. Patients will be divided into two groups: the group that will start supplementary therapy with L-Arginine 3.32g per day orally and the placebo group that will follow the diet and exercise program alone. The aim of the study is to compare the efficacy of L-arginine in delaying the development of type two diabetes and reducing oxidative stress compared to the placebo group.

2. What are the patient groups compared? What is the intervention being tested?

42 patients aged between 20 and 70 years with BMI>25Kg/m2 and pre-diabetes will be included in the study and will be randomized into two groups: the group that will start supplementary therapy with L-Arginine and the placebo group. Patients with moderate-to-severe renal impairment, impaired liver function, hypoalbuminemia, cardio-vascular diseases, who have diseases or are taking drugs that can cause diabetes and obesity, patients treated with antidiabetic drugs or insulin and pregnant women will be excluded from the study. The randomization of patients into the two groups will take place with a ratio of 1:1. 21 patients will be experimentally treated with L-Arginine 1.66g orally twice daily and 21 patients with placebo for 90 consecutive days. You will be drawn to receive the drug or placebo and will therefore have a 50% chance of starting the experimental therapy with L-arginine. Patients randomized to placebo will therefore not take the active substance L-Arginine. Nowadays, there is currently no drug on the market validated to delay the development of type two diabetes in patients with prediabetes and overweight or obesity, but it is currently strongly recommended to follow a low-calorie diet and a physical activity program in order to lose weight. This study is defined as ''double-blind'' as neither the patient nor the investigators will be aware of the group assigned to the patient (L-Arginine VS Placebo) in order not to influence the outcome of the trial in any way. Such methodologies are necessary to avoid biases and obtain valid results.



3. What tests, tests and procedures are planned if I participate in the trial?

Will have to perform an initial visit for an endocrine-metabolic evaluation at the Endocrinology Unit at IRCCS San Raffaele Hospital in order to assess whether all inclusion criteria are met to be enrolled in

the study. Initially, fasting blood glucose and glycated hemoglobin, cholesterol and further blood chemistry tests will be evaluated for oxidative stress markers (AOPP, TBARs, TRAP, Glutathione, interleukin, ESR, CPR). Patients will undergo physical examination and anthropometric measurement of weight, height, waist circumference and waist/pelvis ratio. He will then be randomized to the L-arginine or placebo group for 90 days and then will undergo a follow-up visit between day 91 and 95 during which the investigations performed during the initial visit will be repeated.

For each individual examination or invasive intervention envisaged by the trial, specific consent will be collected at the health act.

4. **What risks can I face if I participate in the trial?**

No side effects are expected to be related to taking L-arginine nor are there any studies that testify to the appearance of side effects after taking L-Arginine. If side effects appear, they will be monitored and recorded by the investigator. Although we believe that the new treatment may delay the development of type 2 diabetes, we cannot rule out that this treatment will be ineffective in you. Any adverse effects on the product of conception have not been reported in the studies. You will still be asked, for the entire duration of taking the drug, to commit to adopting contraceptive methods of sure effectiveness.

5. How will I be informed of any unexpected results following further diagnostic investigations?

From the execution of the analyses envisaged by the experimentation, it is not expected that unexpected results may emerge.

1. Is it useful/necessary to inform my family doctor?

In view of the design of the trial, if you decide to participate, it may be useful to inform your family doctor. To this end, we will give you a letter that you can give to him, in which the procedures of the trial are explained

6. **What will be my commitment and what responsibilities will I have if I decide to participate?**

Scrupulously observe the indications and requests from the health personnel following the trial and ensure attendance at appointments.
Inform your doctor following the trial:

- of all medications you are taking including non-conventional medicine medications,
- any side effects that occur during the trial,
- any visit or hospitalization in facilities other than the investigational center,
- current or past participation in other clinical trials.

Record in the diary all the times the investigational drug is taken at home.
Women are asked to avoid pregnancy or breastfeeding during the trial as harmful effects of the drug on the fetus cannot be ruled out with certainty. If you intend to participate in the protocol, you are expected to commit not to become pregnant during the 90 days of the study in which you will be taking the drug. If you become pregnant, you must immediately inform the doctor responsible for the treatment. Even if you are breastfeeding, you should not participate in this trial
It is not recommended for men to procreate. During the trial, your partner must not become pregnant as harmful effects of the experimental drug on her sperm fluid and therefore on the fetus cannot be excluded. We

therefore invite you to inform your partner of this. If your partner becomes pregnant, you should immediately inform the doctor responsible for the treatment.

7. Will I have to face costs for participating in the trial? Will I be reimbursed for any expenses? Will I receive compensation?

There are no costs to be borne by the Sponsor and Promoter as these are fully covered by the Sponsor/Sponsor. There is also no financial compensation for participation in the trial.

8. What happens if I suffer damage as a result of participating in the trial?

Participation in a clinical trial may involve inconveniences and risks that cannot be determined a priori. For this reason, the clinical trial provides insurance coverage to protect your participation.

In compliance with the laws in force, insurance is provided to cover any damage suffered due to participation in the trial, for the entire period of the same, to cover the civil liability of the investigator and the Sponsor. All procedures related to the study will be covered and monitored by CRA (Clinical Research Associate) sponsored by DAMOR Farmaceutici whose details will be attached.

It should be noted that the current policy does not include:

1. damage caused by the use, use or testing of the following products and/or their derivatives:
   - *Aegeline*
   - *Alosetron;*
   - *Amiodarone;*
   - *Apomorphine;*
   - *Aristolochia*
   - *Astemizole*
   - *Atypical Antipsychotics (products containing Loxapine, or Clozapine, or Olanzapine, or Risperidone, or Quetiapine, in any form);*
   - *Attention Deficit Hyperactivity Disorder Drugs (A.D.H.D.) - (e.g. Metilfenidato, atomoxetine e amphetamine)*
   - *Country mallow (heartleaf)*
   - *Benfluorex*
   - *Bifosfonati (e.g. alendronate, etidronate, ibandronate, pamidronate, risedronate, tiludronate, zoledronic acid, etc)*
   - *Botulinum Toxin Type A e B;*
   - *Bromfenac;*
   - *Bromocriptine;*
   - *Bupropion;*
   - *Butorphanol;*
   - *Canthaxanthin;*
   - *Cerivastatin*
   - *Cisapride;*
   - *Clindamycin;*

- *Clobenzorex*
- *Any contraceptive, contraceptive, RU 486, "day-after-pills" products;*
- *Danthron;*
- *Dexfenfluramine;*
- *Diethylstilbestrol (DES), Stilbestrol;*
- *Dimethylamylamine (DMAA)*
- *Dronedarone*
- *Encainide;*
- *Ephedra (Ma huang, amsania, brigham tea), Cathine (norpseudoephedrine) Pseudoephedrine, Ephedrine,phenylephrine e derivati;*
- *Ethylamphetamine*
- *Fenfluramine;*
- *Flosequinan;*
- *Gadolinium containing contrast agents;*
- *Garcinia (Garcinia cambogia)*
- *Germanium;*
- *Grepafloxacin;*
- *Halogenated 8-Hydroxyquinolines;*
- *Hydroquinone;*
- *Phosphodiesterase inhibitors – (i.e. Sildenafil, Vardenafil, Tadalafil);*
- *Selective COX-2 inhibitors, e.g. rofecoxib, valdecoxib, celecoxib, etc)*
- *Intranasal products containing Zinc*
- *Itraconazole;*
- *kava-kawa (A.G. piper methodistic, they root, they are pepper shrub);*
- *Khat (e.g. Catha edulis, Cat, Chat, Gad, Kaht, Miraa and Tschut);*
- *Kratom*
- *Leflunomide;*
- *Oxycodone / OxyContin;*
- *Mefenorex;*
- *Methadone*
- *Mibefradil;*
- *Nefazodone;*
- *Phenylpropanolamine (PPA);*
- *Phentermine;*
- *Fibre-based products;*
- *Statin products;*
- *Hormone Replacement Therapy Products (H.R.T.);*

- *Products to lighten or brighten the skin;*
- *Serotonin-norepinephrine Reuptake Inhibitors (SNRIs) (e.g. duloxetine, venlafaxine);*
- *Selective Serotonin Reuptake Inhibitors (SSRIs) (e.g. fluoxetine, paroxetine, fluvoxamine, citalopram e tutti i prodotti similari);*
- *Sibutramine;*
- *Sumatriptan;*
- *Tegaserod Maleate;*
- *Terbinafine;*
- *Terfenadine;*
- *Temafloxacin;*
- *Thalidomide;*
- *Theophylline;*
- *Rapacurionium;*
- *Remoxipride;*
- *Retinoids, including all active ingredients and products included in the family of retinoids (by way of example and not limited to: Retinoic Acid; Retinol; Retrinal; Tretinoin; Isotretinoin; Alitretinoin; Etretinate; Acitretin);*
- *Rimonabant*
- *Thiazolidinediones, Pioglitazone, Rosiglitazone, Troglitazone;*
- *Thimerosal/Thiomersal;*
- *Troglitazone*
- *Trovafloxacin; Alatrofloxacin*
- *Transvaginal mesh*
- *Usnea*

2. damage resulting from communicable diseases (e.g. HIV, hepatitis of any kind, TSE, trepenoma pallidum) resulting from organs and/or tissues of human and animal origin, blood products of human and animal origin, bones of human and animal origin, stem cells of human and animal origin;
3. damage resulting from transmissible spongiform encephalopathy (TSE);
4. damage resulting from genetically modified substances or organisms in general and deriving from or resulting from genetic engineering or bioengineering;
5. damages resulting from experiments that are not regularly authorized or carried out in a manner that does not comply with the provisions of the regulations in force or carried out in a manner that does not comply with what is authorized by the competent authorities and the Ethics Committees;
6. congenital pathologies and their aggravations;
7. damage to the genetic heritage caused to individuals and/or their descendants;

8. damages due to non-compliance by subjects with the instructions given by the Investigator/Sponsor;
9. damage due to ineffectiveness of the investigational product;
10. the damage suffered by women who are already pregnant or become pregnant during the Trial and the damage to the health of the fetus;
11. damage attributable to side effects that the state of scientific knowledge allows to identify at the time of carrying out the clinical trial;
12. damage from experiments involving surgical techniques;
13. damage resulting from benzodiazepines;
14. the damage resulting from cannabis and opioid products;
15. the damage resulting from 8 Hydroxyquinoline;
16. damage resulting from natural latex
17. expenses incurred by anyone out of court for searches and investigations aimed at ascertaining the causes of the damage, unless such searches, investigations and expenses have been previously authorized by the Company.
18. damage resulting from communicable diseases, qualified as "epidemics" or "pandemics" by the World Health Organization, including, among these, the so-called COVID 19 for which no coverage is provided with this policy.

It should be noted that, according to the Ministerial Decree of 14 July 2009, the insurance policy does not cover the value exceeding the ceiling and is only applicable to damages for which the claim for compensation has been submitted no later than the period provided for in the policy. However, this limitation does not affect his right to obtain compensation from the person responsible for any damage (to protect the subject of the trial).

9. How will it be processed and who will have access to my health data, including identifying data, during the trial?

Your data, in particular personal and health data and only to the extent that they are indispensable in relation to the objective of the trial and for pharmacovigilance purposes, will be processed in compliance with EU Regulation 2016/679, known as GDPR (General Data Protection Regulation) and Legislative Decree 10 August 2018, no. 101. In practical terms, the documents relating to the participant will be kept in a safe place and will not bear his name in plain text, known only to researchers, but an identification code.

The data, made anonymous, may be subject to control by regulatory bodies and used for scientific publications (journals, conferences).

Your clinical data collected for the purposes of the trial, as well as the results of the tests carried out, will be kept for the time required by the regulations and subsequently destroyed. They will not be destroyed only in the event that a) it is no longer possible to trace them back to their identity, because

they have been anonymized during the experimentation itself; b) in the presence of specific informed consent.

If personal data is transferred to a third country or an international organisation, all the safeguards provided for in Article 46 of GDPR 679/2016 relating to the transfer will be adopted.

Further information is included in the attached data processing consent form.

10. How will they be processed and who will have access to my biological samples taken for the purpose of the trial?

As with its health data, its pseudonymised biological samples (a technique that allows the personal and sensitive data of a natural person to be modified and masked, in order not to make them directly and easily attributable to the same), will also be used for the purposes of the trial.

Once the trial is over, its samples will be destroyed.

11. How will I have access to the results of the trial?

Once the trial has been completed and all the resulting data has been collected, they will be analysed to draw conclusions. The investigators and the Sponsor undertake to make them available to the scientific community.

The standard provides for the possibility of access for participants to the results of the trial. Therefore, you can ask the investigator to inform you of the general results of the trial.

12. Has the trial been approved by the Ethics Committee?

The protocol of the trial that has been proposed to you has been examined and approved by the CET Lombardy 1 Ethics Committee. The Ethics Committee has, among other things, verified that the trial complies with the Standards of Good Clinical Practice and the ethical principles expressed in the Declaration of Helsinki and that your safety, rights and well-being have been protected.

13. Who can I contact for more information about the clinical trial I am invited to participate in?

Dr. Luigi di Filippo difilippo.luigi@hsr.it

14. If I join the trial, who can I contact in case of need?

For any doubts and events that cannot be scheduled or unscheduled during the trial (doubts relating to the treatment in progress, side effects, decision to abandon the trial, etc.), you can contact:

Dr. Luigi di Filippo difilippo.luigi@hsr.it

If you deem it appropriate to report events or facts relating to the trial to which you have adhered to subjects not directly involved in the trial itself, you can refer to the Ethics Committee that approved the CET Lombardia 1 trial, to the Health Management of the Trial Centre or IRCCS San Raffaele Hospital and to the competent authority (AIFA for medicine; Ministry of Health for the Medical Device).

Attachments

- Form for consent to the processing of personal data

Additional documents:

- Letter to the family doctor

9 CONSENT SECTION

(Notes: 1 copy for the participant, 1 copy for the trial manager)

Trial title: Effect of oral L-arginine 3.32 g per day on oxidative stress and influence on beta cell function and insulin resistance. A Phase 3, Randomized, Double-Blind, Placebo-Controlled Exploratory Study in Overweight and Obese Patients With Prediabetes

Protocol Code, Version and Date: L-BIOARG, version 1.0 of 08/10/2024

Trial promoter/sponsor/funding body: IRCSS San Raffaele Hospital

Principal Investigator (*name, affiliation, references*): PROFESSOR ANDREA GIUSTINA

I, the undersigned_____

born/a_____ ___/___/_____

DECLARE

☐ to have received from Dr. _____ exhaustive explanations regarding the request to participate in the research in question, as reported in the information section, part of this consent, of which I was given a copy on _____ _____ (*indicate date and time of delivery*);

☐ that I have been clearly explained and understand the nature, purposes, procedures, expected benefits, possible risks and drawbacks and alternative treatment modalities to the proposed clinical trial;

☐ to have had the opportunity to ask any questions to the study investigator and to have had satisfactory answers;

☐ that they have had sufficient time to reflect on the information received

☐ that he has had sufficient time to discuss it with third parties;

☐ to have been informed that the protocol of the trial and all the modules used have had the favourable opinion of the competent Ethics Committee;

☐ to be aware that the research may be interrupted at any time, by decision of the research manager;

☐ that I have been informed that I will be made aware of any new data that may compromise the safety of the research and that, for any problem or further questions, I will be able to contact the doctors with whom I am being treated;

☐ who for the best protection of my health I am aware of the importance (and my responsibility) of informing my GP of the trial in which I agree to participate. I am aware of the importance of providing all information (drugs, side effects, etc.) concerning me to the investigator;

☐ that I have been informed that the results of the study will be made known to the scientific community, protecting my identity according to current privacy legislation;

☐ you understand that any choice expressed in this consent form may be revoked at any time and without any justification;

☐ that you have received a copy of this consent form.

I therefore declare that

☐ To want ☐ NOT wanting participate in the trial

☐ To want ☐ NOT wanting To be informed of all unexpected news related to my health present or future that may incidentally emerge from the investigations envisaged by the trial, including genetic investigations, when this may result in possible benefits

☐ To want ☐ NOT wanting Be informed of unexpected news related to my health present or future only when this can be useful for my health care or to enable me to make informed reproductive choices

☐ To want ☐ NOT wanting be contacted after the end of the trial to provide information about my health status (applies only to contacts not expected as follow-up from the study protocol)

If applicable:

☐ accept ☐ DO NOT accept the use of contraceptive drugs

_____ ___/___/_____ _____ _____

Full name and surname of the adult patient Date Hour Signature

_____ ___/___/_____ _____ _____

Full name and surname legal representative Date Hour Signature

(N.B. If the patient is unable to read or sign personally, a witness independent of the Investigator and the Sponsor must be present during the entire informed consent discussion. The witness must personally sign and date the informed consent statement after the form itself and any other written information have been read and explained to the subject and the subject has given verbal consent to participate in the study).

In this case:

I, the undersigned..... I testify that dr. ..... exhaustively explained to the sig./sig.ra..... ..... the characteristics of the study in question, as reported in the information sheet attached hereto, and that he/she, having had the opportunity to ask all the questions he/she deemed necessary, freely agreed to participate in the study.

Name and surname in capital letters of the independent witness .....

Date..... Signature of the independent witness .....

STATEMENT FROM THE DOCTOR WHO COLLECTED CONSENT

_____

(Patient's first and last name, place and date of birth)

Trial title: Effect of oral L-arginine 3.32 g per day on oxidative stress and influence on beta cell function and insulin resistance. A Phase 3, Randomized, Double-Blind, Placebo-Controlled Exploratory Study in Overweight and Obese Patients With Prediabetes

Protocol Code, Version and Date: L-BIOARG, version 1.0 of 08/10/2024

Trial promoter/sponsor: IRCSS San Raffaele Hospital

Principal Investigator (*name, affiliation, references*): PROFESSOR ANDREA GIUSTINA

I, the undersigned Prof./Dr. (Name and Surname) _____ in my capacity as Principal Investigator (or delegate of the Principal Investigator)

DECLARE

that the Patient has voluntarily consented to his participation in the trial

I also declare that:

- ☐ have provided the patient with exhaustive explanations regarding the purposes of the trial, the procedures, the possible risks and benefits and its possible alternatives;
- ☐ have verified that the Patient has sufficiently understood the information provided to him
- ☐ have given the patient the necessary time and the opportunity to ask questions about the trial
- ☐ that they have clearly explained the possibility of withdrawing from the trial at any time or of changing the choices made
- ☐ not have exercised any coercion or undue influence in the request for this consent
- ☐ have provided the Patient with information on how the results of the trial will be made known to him/her

_____ _____

Place and date Hour

_____ _____

Name Surname (block letters) of the doctor who provided the information and who has collected consent

Signature (and letterhead)

This form is an integral part of the consent form and must be kept together

to the previous information sheet for informed consent