Patient Information Sheet

Protocol Title: A randomized, multicenter, open-label, phase II trial to evaluate the efficacy and safety of palbociclib in combination with fulvestrant or letrozole in patients with HER2 negative, ER+ metastatic breast cancer (PARSIFAL).

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Study Sponsor: Medica Scientia Innovation Research (MedSIR)

Investigator: *[For site-specific ICF: Insert Investigator's name and contact information (i.e. phone number and address if different from institution address below)]*

Institution: *[For site-specific ICF: Insert institution name and address]*

OVERVIEW

You are being asked to take part in a clinical research study of an investigational drug. Before you agree to take part in this research study it is important that you read and understand this document.

This document describes the purpose, procedures, responsibilities and potential risks and benefits involved in taking part in this clinical trial. In this document you will also find the alternative procedures that are available to you and your right to withdraw from the study at any time without having to give any reasons and without this being detrimental to your health care.

If this document uses any terms you do not understand, ask your doctor or a member of the staff involved in the clinical trial to explain it to you. If you decide to take part in this study, you will be asked to sign this consent form. A copy of this signed form will be given to you to keep.

What is this purpose of this study?

We invite you to participate in this research study because you have been diagnosed with a breast cancer that cannot be treated with surgery or radiation therapy with curative intent (called "advanced breast cancer") but yet your cancer is sensitive to hormonal treatment.

In this study, patients can be treated with the combination of palbociclib plus letrozole or with the combination of palbociclib plus fulvestrant. The main purpose of this study is to find out which of the two combinations is more effective.

Fulvestrant is a drug that has already been approved for the treatment of advanced breast cancer that is sensitive to hormone treatment in postmenopausal women.

Letrozole is a drug that belongs to the group of aromatase inhibitors that has been approved for the treatment of advanced breast cancer that is sensitive to hormone treatment.

Palbociclib is new drug, approved in US in 2015 and in European Union at the end of 2016 to treat locally advanced or metastatic breast cancer. Palbociclib is approved to be used together with an aromatase inhibitor such as letrozole in the first-line treatment of the type of breast cancer you have been diagnosed. Palbociclib has been also approved to be used together with fulvestrant in patients who have previously been treated with a hormonal medicine.

You should know that there are other treatments for the type of breast cancer that you have. The study doctor will discuss with you about the possible advantages and disadvantages of being part of this study as well as other options treatments that you can choose.

This study includes also additional scientific research to investigate DNA, RNA or proteins. The goal of this research is to determine the status of different genes and or proteins that could be used as markers of cell tumour reproduction, and also to assess whether the status of these markers is related to treatment response.

Genetic information affects physical features and health status, so studying the genetic information may help scientist and clinicians to learn more to identify genetic reasons why certain individuals respond differently to drugs or to identify variations of genes that may cause or modify the disease.

In case of your disease, current knowledge links changes or mutation in some genes that prevents them from performing their normal function.

Blood and tissue samples collected in this additional research will be used for multiple studies in DNA, RNA and proteins using different methods. Genes and proteins analyses will include among others Ki67, cyclin D1, cyclin A1, pRb HER2, Cyclin D1 and ESR1.

It will be also studied the pattern of expression of all proteins (proteomics) from the tumoral tissue to compare if this pattern is modified depending on the treatment received and/or if it is modified when comparing tissue before starting the treatment, and at the time of progression.

Who is sponsoring and conducting this research?

This research study is being sponsored globally by Medica Scientia Innovation Research (MedSIR) that is providing financial support to cover the cost of study-specific procedures performed during this study.

Who has reviewed this research?

This study has been approved by *{Name of IRB/EC}*, an organization that is responsible for protecting the rights and safety of patients who take part in research studies.

How many people will take part in the study?

About 486 patients (243 patients in Arm A and 243 patients in Arm B) from different Europe and Middle East hospitals are expected to take part in this clinical trial.

What will happen if I take part in this research study?

You are being asked to take part in this study because you have been diagnosed with ER+ metastatic breast cancer and your doctor thinks that you are a good candidate to receive first line hormonotherapy. Your study doctor will confirm to you whether you meet other clinical criteria necessary to take part in the study. You cannot take part in this clinical trial if you are participating in another research study.

Before you begin the study, you will need to undergo the following tests or procedures to find out if you can be in the study. Some of these tests or procedures may be part of

your regular medical care and may be done even if you do not take part in the study. If you have had some of them recently, they may not need to be repeated.

- Discussion of this study and review and signing of this Informed Consent Form
- Recording of your demographic information, including your age, and race/ethnicity
- Confirm your postmenopausal status, if you have not yet reached menopause, a medicine called a luteinising hormone-releasing hormone agonist should also be given.
- Review of your medical history and any medications (including herbal or dietary supplements) you are taking or have taken within the last 30 days
- Complete physical examination
- Measurement of your height and weight
- Measurement of your vital signs (breathing rate, heart rate, blood pressure, and body temperature)
- The type of tumour you have will be checked: Confirmation ER+ and HER2 – status
- The extent of your disease will be also evaluated by computed tomography -TC- thoracic-abdominal or magnetic resonance -RM- and / or bone scan.
- Electrocardiogram (ECG). An ECG is a measurement of the electrical activity of your heart.
- Collection of about 10 ml of blood for standard laboratory tests (including blood chemistry and blood cells count).
- Assessment of any side effects associated with screening procedures

If you agree, and the study doctor determines that you are a good candidate to participate in the trial, you will be assigned to one of the treatment groups.

If you decide to take part in this research, several samples need to be collected. Participation in this additional research will not result in any changes to the type of treatment you are receiving or will later receive.

If you consent to participate in the study, blood samples will be collected for genetic analysis (up to 30 ml of blood) before first dose of study treatment. These blood samples are in addition to any blood samples that will be drawn for the purpose of your medical care.

In addition, you must consent for collection of tumour tissue from the biopsy done to diagnose your current disease. This biopsy might be part of the standard clinical care or could be done specifically for this research. In case you had been diagnosed of

breast cancer previously and now you the disease has spread to other parts of the body, you must at least provide consent to use the archived tissue sample from the initial tumour. Consent for this archived sample must be also provided even the biopsy of your present disease is available. Tumour tissue samples will be stored in paraffin. If enough tissue is available, part of the samples will be stored frozen as well. If you have started the treatment in the main clinical study already, samples of tumour tissue from the biopsy done before you started the treatment can be retrieved for this research.

During study treatment

If you are finally included in the study, you will be randomly assigned to receive palbociclib plus fulvestrant or palbociclib plus letrozole. Random assignment means that you will have a 50% chance of being assigned to each of the two treatment groups. Neither you nor your doctor can choose the treatment arm in which you participate.

Palbociclib is taken in the two treatments arms. You will start treatment with capsules of palbociclib at 125 mg. Palbociclib capsules should be taken orally every day from Day 1 until Day 21 of every 28-day cycle.

Patients in Arm A will receive also fulvestrant 500 mg/5mL i.m. Injection. Fulvestrant should be administered on Days 1, 14, during the 1st cycle (28-day cycle) and on Day 1 for the next cycles.

Patients in Arm B will also receive letrozole 2.5 mg tablet orally once daily, every day from Day 1 till Day 28 of a 28-day cycle.

It is important to take palbociclib with food. Both, palbociclib and letrozole should be swallowed whole with a glass of water and should not be chewed or sucked. You are strongly encouraged to take the capsules at the same time each day. Fulvestrant is administered intramuscularly once a month.

Remember to follow the additional instructions from your doctor and return all remaining medication during each cycle as well as the empty blisters and containers.

During the treatment period you will be asked to attend to the clinic at least once every 4 weeks where you will undergo the tests and procedures described below. All these procedures are part of the standard clinical care for your disease, unless it is indicated otherwise

During all the study visits, you will be asked about any changes in your health and/or in your home treatment since the previous visit. The treatment side effects will be written down exactly as you tell to your doctor.

You will have a physical check-up including weight and vital signs.

A routine blood test (approximately 10 ml of blood) will be done by the study personnel to check the number of cells in your blood and how well your liver and kidneys are working. An additional, blood test to check the number of blood cells (approx. 5 ml of blood) will be done on day 14 during cycle 1 and 2.

The extent of your disease will be also evaluated by computed tomography -TC- thoracic-abdominal or magnetic resonance -RM- and / or bone scan every 12 weeks.

An ECG will be repeated every 12 weeks to check the proper cardiac function.

After 2 and 12 weeks of treatment a new blood sample of approx. 30 ml will be collected for pharmacogenetic studies.

How long will I be in the study?

You will continue to participate in the present study until trial objectives regarding the efficacy decision criteria are met. You will continue to receive the study treatment until the confirmation of progressive disease, unless treatment has to be interrupted because your doctor considers it is harmful or have unacceptable side effects.

In case of tumour progression, a new blood sample (up to 30 ml) will be collected at the time of progression for pharmacogenomics research purposes and a new biopsy from metastatic lesions will be also performed, whenever possible. This biopsy might be done specifically with research purposes.

In case you consent for collection of tumour tissue sample, a biopsy to obtain tumour tissue will be performed, whenever possible. This biopsy might be done specifically with this research purpose.

If the treatment you were receiving is stopped, you will be followed every 6 months from the last dose of investigational product. Data regarding your condition as well as new anti-cancer therapy information you could be receiving will be collected.

If you have a serious side effect during the study, the study doctor will ask you to visit the clinic for follow-up examinations, even after you have completed your regular study visits.

What are my responsibilities?

As a participant in this trial, you have certain responsibilities that will help to ensure your safety is properly guaranteed during the study. These responsibilities are:

- ✓ Keep your study appointments. If you cannot keep an appointment, contact your study doctor or study staff to reschedule as soon as you know that you will miss the appointment. Tell your study doctor or study staff about any medications you are taking.
- ✓ Inform your doctor or any study staff about any side effects, other doctor visits, or hospitalizations that you may have whether or not you think they are related to the study treatment.
- ✓ Complete a patient diary to record the information on the study medication you are taking.
- ✓ Tell your study doctor if you have been in a research study in the last 30 days or are in another research study now. While participating in this research study, you should not take part in any other research project.
- ✓ Inform your doctor if you do not wish to continue receiving treatment as part of the clinical trial. In this case, you will be asked to attend a final safety visit.
- ✓ Inform your doctors that you are taking part in this study.
- ✓ Carry with you at all times during the study a card that states that you are taking part in this study.

Will I be told about new information?

During the study, you will be told in a timely manner about new information or changes in the study that may affect your health or your willingness to continue in the study. If based on this potential new information, you agree to continue in the study, you will be asked to sign an updated consent form.

Are there benefits to taking part in the study?

Taking part in this study may or may not involve any type of direct medical benefit to you. While doctors hope that combining palbociclib to standard hormonal treatment

could be more useful against breast cancer compared to the usual treatment, there is no proof of this yet.

It is possible that your participation in this study could benefit future breast cancer patients thus contributing to the development of possible future treatments and can help doctors to learn more on this condition.

What side effects or risks and discomforts can I expect from being in the study?

Although all medication is carefully studied before being administered to humans, adverse events may occur.

Besides the side effects described below, there may be other side effects that are currently unknown. You or your legal representative will be properly informed if new information on the medication used in this study comes to light that may be relevant to you continuing to take part in the trial. If your doctor decides to stop the study treatment because of an adverse reaction you will be offered alternative treatment your doctor considers more appropriate in your case.

Risks and side effects related to fulvestrant

Fulvestrant is an approved and marketed treatment for metastatic breast cancer and it is a drug commonly used in the routine clinical practice.

The reported adverse reactions associated with the treatment with fulvestrant 500 mg are:

- >10%: injection site nerve damage (numbness, tingling, weakness), asthenia, nausea, increase in liver enzymes, skin rash, hot flashes, muscle, joint and bone pain, hypersensitivity reactions.
- Between 1 to 10%: headache, vomiting, diarrhoea, anorexia, urinary tract infection, and elevated bilirubin.
- Other infrequently (< 1%) adverse reactions reported as drug-related include hepatic failure, hepatitis, increased in Gamma-glutamyl transferase (liver enzyme).

Risk and side effects related to Letrozole

- > 10 % or more: Bone problems such as bone fractures or osteoporosis, general feeling of being unwell, high levels of cholesterol in the blood, hot flushes, increased sweating, joint pain, tiredness, weakness.
- Between 1 to 10%: angina or worsening of angina, appetite gain, bone pain, cerebrovascular problems, constipation, depression, diarrhoea, dry skin, feeling dizzy, hair loss, headaches, heart attack, heart problems, indigestion, loss of appetite, muscle pain or tenderness, nausea, oedema of the extremities, raised blood pressure, skin rash or rashes, stomach pain, stroke, vaginal bleeding, vomiting, weight gain.
- Between 0.1 to 1%: abnormal, laboratory test results, arthritis, blood and bone marrow problems, blurred vision, breast pain, breathing difficulties, carpal tunnel syndrome, cataracts, cough, difficulty sleeping, dry mouth, dry mucous membranes, eye irritation, faster heart rate, feeling anxious, feeling irritable, feeling nervous, fever, hypoesthesia, inflammation of the mouth, itching, memory problems, oedema, palpitations, paraesthesia, sleepiness, taste changes, thirst, thromboembolism, thrombophlebitis, tumour pain, urinary tract infection, urinating more often, urticarial, vaginal discharge, vaginal dryness, weight loss.
- Rare: pulmonary embolism, thrombosis.

The frequency of these side-effects is unknown: anaphylactic reactions, angioedema, erythema multiforme, liver problems, and toxic epidermal necrolysis, trigger finger.

Risk and side effects related to palbociclib

Palbociclib has been given to approximately 1380 patients with breast cancer who received palbociclib together with hormonal treatment in Pfizer sponsored clinical trials.

The following side effects have been observed in clinical trials with palbociclib when given together with hormonal therapy, letrozole, in patients with breast cancer:

The following side effects have been reported:

- 30% or more: decreases in neutrophil blood cells (may increase the risk for infection), decreases in white blood cells (infection fighting cells), infection, fatigue
- 10 to <30%: decreases in haemoglobin (may cause weakness), decreases in platelets (may cause bleeding and/or bruising), inflammation of the mouth,

diarrhoea, constipation, nausea, vomiting, joint pain, back pain, pain in hands and feet, hair loss, rash, cough, shortness of breath, headache, dizziness, decrease appetite, hot flush, insomnia (inability to sleep)

- 5 to <10%: abdominal pain, indigestion, dry mouth, fever, asthenia (general weakness), swelling of hands and feet, irritation or sores in the lining of hollow organs like mouth, throat, stomach, bowels; pain, influenza (flu) like illness, muscle pain, pain in the muscles and bone including around the chest, muscle cramps, increases in blood liver markers that may indicate liver damage, dry skin, itching, mouth/throat pain, nosebleed, impaired sense of taste, high blood pressure, depression, fall

The following adverse events have been reported in clinical trials with palbociclib when given together with hormonal therapy, fulvestrant, in patients with breast cancer:

- 30% or more: decreases in neutrophils (may increase the risk for infection), fatigue, nausea
- 10 to <30%: decreases in white blood cells (infection fighting cells), decreases in haemoglobin (may cause weakness), headache, diarrhoea, constipation, hair loss, vomiting, hot flashes, cough, back pain, decreased appetite, joint pain, decreases in platelets (may cause bleeding and/or bruising), pain in hands and feet, inflammation of the mouth, dizziness, shortness of breath, common cold, fever, mouth/throat pain
- 5 to <10%: rash, insomnia (inability to sleep), indigestion, abdominal pain, swelling of hands and feet, upper respiratory tract infection, muscle pain, muscle spasms, weakness, increases in blood liver markers such as alanine aminotransferase and aspartate aminotransferase, musculoskeletal pain, impaired sense of taste, dry mouth, injection site pain, urinary tract infection, nosebleed, itching, influenza (flu) like illness, high blood pressure, increases in tear production (watery eyes), blurred vision, depression, dry skin.

The following side effects have been reported in <5% of the patients with breast cancer in clinical trials with palbociclib given together with hormonal therapy, fulvestrant or letrozole. Although uncommon and infrequent, they are still deemed important and include: general fever, fever associated with dangerously low levels of a type of white blood cells (neutrophils), infections that inflames the air sacs in one or both lungs, urinary tract infection, decreases in lymphocyte blood cells (infection fighting cells and neutrophils), blurred vision, increased tearing, dry eye, decreased number of healthy

red blood cells, bacterial infections spreading underneath the skin surface, increases in blood liver markers such as alanine aminotransferase and aspartate aminotransferase, influenza, inflammation of the appendix, acute fever with large raised red patches on the skin caused by a bacterial infection, pharyngitis, infections which can extend to multiple organ systems, sinusitis, infections due to the bacteria *Staphylococcus aureus*' presence in the blood, upper respiratory tract infection, urogenital tract infection, and flat or raised red bump on the skin.

Palbociclib is also being evaluated in a number of clinical trials run by independent investigators in a variety of tumour types. The side effects reported in these studies to date ere similar to those mentioned above.

Serious and life-threatening infections have been observed in some patients treated with palbociclib.

Possible risks and discomfort associated with drawing blood

During this study, small amounts of blood will be drawn from a vein and used for tests that allow your study doctors to see how you are doing. Drawing blood may cause pain where the needle is inserted, and there is a small risk of bruising or infection at the place where the needle is inserted. Some people experience dizziness, upset stomach, or fainting when their blood is drawn. Precautions will be taken to avoid these side effects. Whenever possible, blood for this additional pharmacogenomics research discussed above will be drawn at the same time as samples for other required laboratory tests. If not, an additional needle stick may be required.

Risks associated with obtaining biopsies

Tissue biopsies will be obtained during the study. The risks associated are bleeding, pain, bruising, perforation or penetration of the needle into the vein which may produce a colour change, bleeding at the puncture site of the needle into the vein, infection and blood clots. All precautionary measures will be taken to ensure that the biopsy procedure will have the smallest chance of possible risks.

Risks associated with unauthorised use of data in pharmacogenomics research:

Strict privacy and confidentiality procedures for this research have been adopted (See, "How will health information that identifies me be used and disclosed?" Section). However, there is still very small risks associated with a loss of privacy or

confidentiality. For example, if your identity as a participant in pharmacogenomic research or your identifiable genetic or health information were disclosed to unauthorized persons, there is the possible risk of discrimination by employers or insurance providers.

Possible risks and discomfort associated with CT scans

CT scans are special X-ray tests used to study the internal organs and bones of your body, and they are necessary for measuring your response to this treatment. You would likely undergo these scans even if you were not participating in this research study because your doctor would need to monitor your disease.

You will be exposed to radiation from CT scans approximately every 12 weeks. Scientists disagree on whether radiation doses at these low levels are harmful. A possible effect that could occur at doses associated with this study is a slight increase in the risk of developing cancer later in life. Since the effects of radiation can build up over time, it is important to know of your past radiation exposure. If you have been exposed to radiation through CT scans, X rays, or other means in the past 12 months, please inform study personnel. If it is determined that your prior radiation exposure exceeds current guidelines, it is possible that you will not be allowed to participate in this study.

As part of the CT scan, a contrast agent may need to be taken by mouth and/or injected into your vein to make certain organs and disease sites visible on the scan. Oral contrast may cause side effects such as nausea, constipation, diarrhoea, and abdominal bloating. Pain, bruising, redness, swelling, or infection may occur at the site where a needle is inserted to administer the contrast material into your vein. It is normal to experience a warm, flushing feeling when the contrast material is given. You may have an allergic reaction to the contrast material that may cause rash, hives, shortness of breath, wheezing, and itching, and rarely may cause your heart to stop beating ("cardiac arrest"). The use of contrast material during these tests would be a normal part of measuring your response to therapy, even if you were not participating in this research study.

Possible risks and discomfort associated with MRI scans

MRI scans are specialized imaging procedures that are necessary for measuring your response to this treatment. For most patients, the risks or side effects associated with undergoing MRI are minimal. An MRI scan does not involve ionizing radiation like

conventional X rays. Instead, images are generated using a magnetic field and radio signals. Because an MRI scanner uses strong magnets, you cannot have any metal implants in your body to have an MRI scan. People with an artificial heart valve, metal plate, pin, or other metallic objects in their body (including gun shot or shrapnel) are not eligible for MRI scans. Study personnel will ask you questions to make sure you can safely have an MRI scan.

There may be some anxiety and claustrophobia (fear of being in small places) associated with the scanner. Staff at the imaging centre use techniques to help reduce these feelings in patients. Your study doctor may also prescribe mild sedatives or anti-anxiety drugs to help manage your symptoms. As part of the standard MRI scan, a contrast agent containing gadolinium is injected into your vein to enhance visibility. The risks associated with the contrast agent include mild nausea, headache, hives, temporary low blood pressure, chest pain, back pain, fever, weakness, and seizures. There have been reports of a severe and potentially fatal condition known as nephrogenic systemic fibrosis (a scarring condition that can lead to kidney failure) that has occurred in some patients who received gadolinium-based contrast agents. This has not been seen in patients with normal working kidneys or mild problems in kidney function. Prior to study entry, your study doctor will run tests to determine if your kidneys are working properly to make sure that the contrast agent is safe for you.

Will I be paid to participate in this study?

There will be no charge to you for your participation in this study. The study drug, study-related procedures, and study visits will be provided at no charge to you.

Examinations, scans, laboratory tests, and other medical procedures and treatments that would routinely be needed to monitor and treat your illness are known as “standard of care” services. Certain standard of care services and treatments will be performed as part of your participation in the study. Charges for some or all of these standard of care services may be billed in the usual manner to you or the hospital you are being treated. If you have any questions about costs to you that may result from taking part in this research study, please speak with the study team.

The costs for research-related services will be covered by the study sponsor.

Study medications (fulvestrant, letrozole and palbociclib) will be provided at no cost to you.

Information from this study may lead to discoveries and inventions or development of a commercial product. You and your family will not receive any financial benefits or compensation from or have rights in any developments, inventions, or other discoveries that might come from this information.

What other options do I have besides participating in this study?

If you do not want to be part of this study, your treatment as prescribed by your doctor will still continue and your healthcare will not be affected in any way.

You should discuss treatment alternatives that may be right for you with your doctor.

If you decide to take part in the trial but the treatment does not manage to control your disease your doctor will provide another treatment from among those currently available that, according to his/her criteria, is most appropriate for your case.

Sample collection, storage, distribution and destination

Samples (blood and tumour tissue for pharmacogenomics research will be sent to a central sample storage facility (MARBiobanc) located at IMIM (Hospital del Mar Medical Research Institute. Barcelona)

Sub-group of samples will be used for the analysis planned in the study.

In addition, as scientific discoveries could happen in the future, samples collected now could be useful for future studies.

For this reason, if you agree to do so, samples not used on the analysis planned in the present study will be maintained in a research line collection. In this case, your samples can be used for future research in breast cancer for analysis not strictly related to the objectives of the current research. The samples will not be used for hereditary genetic studies analysing genes giving higher sensitivity to cancer or other diseases.

Samples will be maintained up to 15 years. When (or before) the 15-year period ends, your samples will be either destroyed or anonymized and transferred to a biobank.

The biobank used for the study samples is a public non-profit organization that gathers various biological samples collections for biomedical research purposes.

How will health information that identifies me be used and disclosed?

As part of this research study, your study doctor, nurses, and other {Study Site} staff will collect and record medical and personal information about you, such as information about your general health, how you have responded to the study treatment, any side effects you may have experienced, and the results of any tests performed during the study. The information collected about you will be held by {Study Site}, {Name of CRO}, and MedSIR. This information will remain part of the study data collected in order to protect the integrity of the study. Your participation in this study should be specified in your medical records.

The Study Sponsor undertakes to comply with Regulation (EU) 2016/679 of the European Parliament and of the Council, of 27 April 2016, on the protection of natural persons with regard to the processing of personal data and on the free movement of such data and repealing Directive 95/46/EC (hereinafter, the “General Data Protection Regulation”).

Both the Institution and the Study Sponsor are responsible for the processing of your data and undertake to comply with the data protection regulations in force. The data collected for the study will be identified by a code, so that no information that can identify you is included, and only your study doctor/collaborators will be able to relate this data to you and your medical history. Your samples collected for pharmacogenomics research will be identified with the same code number that identifies your data in the clinical part of the study. Pharmacogenomics research is not intended to provide you with clinical information. The data that is maintained in databases and created during pharmacogenomics studies is for research purposes only. MedSIR will not initiate the return of any of the genetic information to you or your doctor. Information resulting from the research will not be entered into your medical records. Therefore, your identity will not be disclosed to anyone else except the health authorities, when required or in cases of medical emergency.

The Research Ethics Committees, the representatives of the Health Authority in inspection matters (foreign health authorities), and the personnel authorised by the Study Sponsor (study monitors, auditors), may only have access to verify personal

data, clinical trial procedures and compliance with good clinical practice standards, always maintaining the confidentiality of the information in accordance with current legislation.

The data will be collected in an investigation file under the responsibility of the Institution and processed as part of its participation in this study.

The Investigator and the Study Sponsor are required to retain the data collected for the study for at least twenty-five (25) years after its completion. Subsequently, your personal information will only be retained by the Institution for your health care and by the Study Sponsor for other scientific research purposes, if you have given your consent to do so, and if permitted by applicable law and ethical requirements. In the latter cases, the Study Sponsor will take appropriate measures to ensure the protection of your privacy and will not allow your data to be cross-checked with other databases that may allow to identify them.

In accordance with data protection legislation, you may exercise your rights of access, rectification, erasure ("right to be forgotten"), restriction of the processing of data that is incorrect, request a copy of or transfer to a third party the data you have provided for the study (data portability), and the right to object and not be the subject of a decision based solely on automated processing, including profiling. To exercise your rights, please contact the principal investigator of the study or the Data Protection Officer of the Institution at {email address: ……}. We remind you that data cannot be deleted even if you stop participating in the trial, to ensure the validity of the investigation and to comply with legal duties and medication authorization requirements. You also have the right to contact the Data Protection Agency in your country if you are not satisfied.

If you decide to withdraw your consent to participate in this study, no new data will be added to the database, but those already collected will be used.

After all of the participants in this study have completed their participation and the data have been analysed and are available to the investigator, you have the right to ask the Investigator for information collected during your participation in the study.

If we transfer your encrypted data outside the European Union to entities in our group, to service providers or to research scientists working with us, your data will be

protected by safeguards such as contracts or other mechanisms set up by the data protection authorities. If the participant wishes to know more about this, he/she can contact the Data Protection Officer of the Study Sponsor dpo@medsir.org.

A clinical study report containing the results of this trial will be made available to anyone who requests a copy. Before this report is provided, additional steps will be taken to protect your information from being linked to you. If information from this study is published in a medical journal or presented at scientific meetings, you will not be identified by name, picture, or any other personally identifying information. It is possible that this information is used and processed in scientific or medical research projects related to the drug used in this trial (palbociclib). You can request to be provided with general information about research studies where your data is used.

A description of this clinical trial will be available at http://www.ClinicalTrials.gov., the information will be also available in www.clinicaltrialsregister.eu [Additional web sites as per local regulations]. These web sites will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

By signing this form, you agree to participate in this trial and agree that your personal data are used in the described conditions.

What happens if I change my mind?

Your participation in this study is voluntary. You can choose not to take part in this study at the beginning or at any time during the study, without having to give any reasons. Your decision will not have a negative effect on your present or future health care. That is, you will not receive any penalty or loss of medical benefits which otherwise you would have been entitled to.

If you wish to withdraw from the study, you should contact your study doctor. He/she will tell you the best way to withdraw from it. In this case you will be asked if your decision is related to any side effect.

The study doctor may continue to use the information collected about you prior to your withdrawal from the study. The information already sent to the study sponsor cannot be withdrawn.

At any time, the study doctor or the MedSIR group may discontinue your participation in this study without your consent. Some reasons for this to happen include: you are not following the doctor´s instructions or if, in the opinion of the doctor, either hormonotherapy (fulvestrant or letrozole) or palbociclib are not being effective drugs, are harmful or have unacceptable side effects, or other reasons at the discretion of the doctor.

If you withdraw from the study, or if it finishes, you will stop receiving the study drug and to ensure your safety, you will be asked to take the required medical tests and follow-up, to assess your health and safety.

MedSIR shall be entitled to retain and use any research results that were obtained prior to your withdrawal of consent. However, if you withdraw your consent and samples are not analysed or are partially analysed, the non-analysed samples or the part of the samples that are not analysed will be destroyed, if you request to do so, but the results obtained from the part of the sample already analysed before you withdraw consent will be retained.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, Dr. {Name}, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him or her at [*Include a 24-hour phone number, if available]*

If one is available

MedSIR will pay for the reasonable costs of immediate care for any physical injury to you that specifically results from the study drug

MedSIR as sponsor of the clinical trial is liable for damage to your health resulting from injury caused by the study treatment and holds appropriate and adequate insurance to cover this study related damage.

There is a policy of liability insurance that covers any damage you may suffer as a result of your participation in this trial, in accordance with the regulations currently in force [include reference to applicable local regulations]). that covers the legal civil liability of the policy holder, as Sponsor of the trial, of the investigator and his staff, the hospital or the site where the study is conducted and their titular, and that will provide

you with the compensation and indemnity in case of impairment of your health or injuries that might happen in relation to the participation in this trial.

This insurance has been taken out with the company [XXXXXXX]

You understand, however, that you have not waived any of your legal rights by signing this consent form.

Who to contact to ask questions or to report a possible injury or an adverse event related to this clinical research?

If you have any questions regarding your participation in this study or if you consider that you have experienced an injury related with this clinical trial or an adverse event related to the study drugs you can contact to:
Dr._____

Contact phone _____

You will receive a card indicating that you are participating in this study. The card will include the name and phone number of the study doctor. Please have this card with you at all times, as long as you remain in the study.
For questions about your rights while taking part in this study, or if you feel that you have not been informed enough about your privacy rights about your health information, or you feel that the privacy of your health information has not been protected, you can contact your doctor.

[Optional text as per country/centre practice] You may also contact {Study Site}'s Institutional Review Board or Ethics Committee (a group of people who review the research to protect your rights) at {telephone number}

INFORMED CONSENT FORM

I was informed about the study and had my first discussions with the study doctor or research staff about that information on Date _____

I have read and understand the information in this informed consent document.

I have had an opportunity to ask questions and all of my questions have been answered to my satisfaction.

I voluntarily agree to take part in this study. I do not give up any of my legal rights by signing this consent document.

I have been told that I will receive a signed and dated copy of this document.

I also agree to

☐ Samples not used on the analysis planned in the present study will be maintained in a research collection line. My samples can be used for future research in breast cancer for analysis not strictly related to the objectives of the current research.
☐ Samples not used beyond the storage period (up of 15 years) are transferred to a biobank (if box is unticked non-used samples will be destroyed).
.

_____

Printed name of study participant

_____

Signature of study participant Date of signature[1]

PERSON OBTAINING CONSENT

_____

Printed Name of the Person Conducting the Consent Discussion

_____ _____

Signature of the Person Conducting the Consent Discussion[2] Date of signature

CONSENT FOR STUDY PARTICIPANT WHO CANNOT READ

The study participant has indicated that she is unable to read. One or more members of the study team read the consent document to the study participant, discussed it with the study participant, and gave the study participant an opportunity to ask questions.

_____

Printed name of impartial witness[3]

_____ _____

Signature of impartial witness Date of signature[1]

☐ Not applicable (*Check this box if the Signature of an impartial witness is not required. Signature of an impartial witness is required if the subject or subject's legally authorized representative cannot read.*)

(1) *Subject / impartial witness must personally date their signature.*
(2) *The investigator, or a suitably qualified and trained person designated by the investigator to conduct the informed consent process, must sign and date the consent document during the same interview when the subject signs the consent document.*
(3) *Impartial Witness: A person, who is independent of the study, who cannot be unfairly influenced by people involved with the study, who attends the informed consent process if the subject cannot read, and who reads the informed consent and any other written information supplied to the subject. Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance.*