CLINICAL STUDY INFORMATION LEAFLET

A Phase II, double-blind, placebo-controlled, randomized study to assess the efficacy, safety and tolerability of Lymfactin® (AdAptVEGF-C Adenoviral Vector) in combination with a surgical lymph node transfer for the treatment of patients with secondary lymphedema associated with the treatment of breast cancer.

Invitation for the participation in the clinical study

You are invited to participate in a clinical study in which the efficacy, safety, and tolerability of the investigational product Lymfactin® is assessed in patients with lymphedema associated with breast cancer treatment (so called secondary lymphedema). Based on the diagnosis of your physician we have estimated that you would be a suitable candidate for the study. This information leaflet describes the study and your role in it.

Your participation is voluntary

Participation in this study is voluntary. You can decline from participating, discontinue your participation, or withdraw your consent without providing any reason at any point of the study without it affecting your right to receive the treatment you need.

You do not need to participate in this study to receive treatment. Your physician will inform you about the treatment options for your disease.

Please take the time to read this information leaflet carefully. If you have any questions, please feel free to contact the investigator or other study personnel. You can find their contact information at the end of this document. If you decide to participate in this study, you will be asked to sign the consent form on the last page.

Study sites and sponsor of the study

The sponsor of this study is the Finnish drug development company Herantis Pharma Plc.

The study is conducted at four locations in Finland. The principal investigator for the study is Specialist in Plastic Surgery, MD, PhD Anne Saarikko (HUS, Helsinki). The other investigators include Specialist in Plastic Surgery, MD, PhD Sinikka Suominen (Töölö hospital, Helsinki), Specialist in Plastic Surgery, MD, PhD Pauliina Hartiala (Tyks, Turku), Specialist in Plastic Surgery, MD Juha Kiiski (Tays, Tampere) and Specialist in Plastic Surgery, MD, PhD Eija Suorsa (Oys, Oulu). In addition, the study is conducted at two study sites in Sweden.

The register holder for the study is Herantis Pharma for such collected information that does not contain names or birth dates (i.e. coded or anonymous information), and the aforementioned hospitals for information that contains names and birth dates (i.e. non-coded information). The register holders are responsible for keeping the collected personal information confidential and for handling the information in accordance with legislation.

Background, purpose and overview of the study

The aim of this clinical study is to assess the efficacy and safety of the investigational product Lymfactin® in the treatment of secondary lymphedema when combined with the conventional treatment i.e. surgical lymph node transfer. The effects of the treatment on lymphedema, the possible side effects affecting the patient, and the patient's quality of life will be monitored. Additionally, the distribution of the investigational product in the body will be examined and different methods to assess the symptoms of lymphedema will be compared.

Lymfactin® is a novel type of drug compound, a so-called gene therapy product, which carries a desired gene (genetic factor) into the patient's body to help it produce a therapeutic compound. Lymfactin® is based on the widely occurring natural adenovirus. The natural adenovirus causes for instance respiratory infections (common cold) in humans. Drug compounds based on the adenovirus have been developed for over a decade and investigated in hundreds of clinical studies. However, adenovirus-based drugs are not in routine use and their long-term effects are therefore still unknown. In the case of Lymfactin® the adenovirus is modified in a way that renders it unable to divide and hence unable to cause an infection. Additionally, a natural human gene has been inserted in the virus through genetic modification. This gene produces the vascular endothelial growth factor C (VEGF-C), which is essential for the growth of lymphatic vessels. Hence, the purpose of the Lymfactin® product is to enhance the mechanism of your body to grow new lymphatic vessels and thereby repair local damages of the lymphatic system and incorporate the transferred tissue in the lymphatic system. The combination of surgery and Lymfactin® aims to repair your damaged lymphatic system and thereby decrease the lymphedema in your arm.

Lymfactin® has earlier been studied in a clinical study in humans in Finland. Two different doses of Lymfactin® were tested in that study, with the smaller dose comprising of ten billion (10^{10}) viruses and the higher dose of a hundred billion (10^{11}) viruses. The doses were typical for this type of a product and were safe based on earlier animal studies, which had been conducted following regulatory requirements. Fifteen patients participated in the study, in which the first three patients received the smaller dose and the twelve last patients the higher dose of Lymfactin®. Based on the study, both doses of Lymfactin® were well tolerated and safe, and the higher dose of one hundred billion viruses was selected for this Phase II clinical study.

We are requesting people suffering from breast cancer treatment associated lymphedema to participate in the study. The patients must be between 18 and 70 years old. A total of 40 patients will be recruited in the study in Finland and in Sweden.

Study methods and procedures

The treatment provided in the study includes the administration of the study product during a surgical procedure. In the surgery, your own soft tissue in the groin area, which contains lymph nodes, is removed and used as a lymph node transplant into which the study product will be injected. After the injection the tissue will be implanted into the armpit of the damaged arm. For some patients, this can be combined with a breast reconstruction surgery.

The study will be conducted as a *placebo-controlled* study. This means that half of the patients participating in this study will receive the investigational product Lymfactin® during the surgery whereas the other half will receive a placebo solution (i.e. physiological 0.9% water-saline solution which approximates to the human blood). The dosing will be double-blinded, which means that you are randomly chosen to receive either Lymfactin® or placebo and neither you nor the physician will know, which product you receive. In either case you will receive the surgical treatment, which is a

conventional treatment for lymphedema. Neither your physician nor anyone else can affect whether you will receive placebo or Lymfactin®.

The comparison to placebo is necessary for an impartial assessment of the efficacy of Lymfactin® in the treatment of lymphedema. The double-blinding ensures that the assessment of the study results is not impacted by the awareness of having received Lymfactin®. Lymfactin® or placebo will be administered only once during the study along with the earlier described lymph node transfer surgery.

The participation in the study lasts for approximately 24 months. The study comprises of 14 study visits to the hospital. The surgery is the major study visit throughout which you will need to stay at the hospital for 5-7 days. Additionally, the state of your health will be followed up three and five years post-surgery. The personnel engaged in the study may also contact you by phone. You can find additional information about the study visits and the related procedures, such as imaging and samples to be taken, in the attached study schedule.

Since the effect of the study product Lymfactin® is not entirely known, women who are pregnant, breast-feeding, or planning pregnancy cannot participate in this study. From the beginning of the actual study and until 6 months post-surgery, women and men of fertile age participating in the study must use reliable birth control. The investigator will discuss with you about suitable prevention methods if necessary.

Your regular medication should remain unchanged from 14 days pre-surgery until 30 days post-surgery. Only the use of anti-inflammatory drugs that belong in the class of so-called COX-2 inhibitors must be discontinued two weeks before the surgery and their use can be continued again four weeks after surgery at earliest. The most common anti-inflammatory drugs such as ibuprofen, naproxen, and diclofenac are not COX-2 inhibitors.

All changes in your medication during the study, such as starting the use of new drugs or a change of dosage, should be discussed with the investigator. In case you visit another physician, you need to inform him or her about your participation in this study.

The potential benefits of the study

It is possible that participation in this study will not be of any benefit to you. Since it is only the second clinical study with Lymfactin®, its possible efficacy is still unknown. However, the study helps assess the safety and efficacy of the combination of Lymfactin® and a lymph node transfer surgery, which may help develop a better treatment for lymphedema than is currently available.

The implantation of lymph nodes into the armpit of your damaged arm and the possible formation of new lymphatic vessels may relieve your lymphedema and hence improve your wellbeing.

During the study you will have medical examinations and you will be informed about health information that may occur and is relevant to you.

The possible side effects and inconveniences caused by the study

The most common, however rare, expected side effects are related to the lymph node transfer surgery. Such possible side effects are wound infections in the groin, armpit, and breast, or bleeding, slow wound healing, and necrosis (tissue damage) or partial necrosis of the transplant. Also, edema, i.e. accumulation of tissue fluid, in the armpit as well as numbness and wound pain in the groin are

possible. The surgery-related risk for developing lymphedema in the lower limb is theoretical, i.e. it is very unlikely to occur.

Also, the investigational product Lymfactin® may cause side effects. Since Lymfactin® is still in the development stage it may be associated with yet unknown side effects. Fever and flu-like symptoms may occur as side effects, and liver enzymes might be temporarily elevated. The wound at the dosing site at the axillary area (armpit) may still secrete wound fluid after you have been discharged from hospital, and the fluid could contain the therapeutic virus. To minimize the theoretical risk of infection, you and everyone living in the same household with you should ensure good hygiene in the form of washing hands carefully. You will receive wound care and hygiene related instructions upon discharge from the hospital.

There is also a theoretical risk that the vascular endothelial growth factor C, VEGF-C, would contribute to the formation of malignant tumors. The risk is considered remote since the amount of VEGF-C in the study is low, the effect is short-lived (few days) and localized to a small area. Additionally, Lymfactin® is not administered directly to the damaged area but to the lymph node transplant that has surgically been transferred from the groin area. The existence of tumor cells in the transplant is unlikely. The Finnish Medicines Agency Fimea has assessed the safety of Lymfactin® and has granted permission for this clinical study based on this assessment.

Participation in the study may also cause unexpected side effects.

If new relevant information regarding your safety is obtained about the investigational product during the study, the investigator will immediately contact you and discuss with you whether you would like to continue in the study.

Confidentiality and data protection

If you participate in this study, your personal data, including information about your health, will be processed for the purposes of the clinical study on a medicinal product. Grounds for processing personal data is a research purpose in the public interest. This means that even if you decide to withdraw your consent, your personal data can still be processed in connection with this study if it is essential to ensure the quality of the study or the safety of the investigational product (including tasks related to monitoring, auditing and archiving). You will be given our privacy statement where you can find more detailed information about the processing of your personal data and your rights related to the processing.

[References: Article 6, paragraph 1(e) and article 9, paragraphs 2(i) and 2(j) of the EU's General Data Protection Regulation 2016/679 and section 6a of the Finnish Medical Research Act (488/1999)].

Only the personnel engaged in this study will know your identity, and they are all legally required to maintain complete confidentiality at all times. All information that concerns you and your samples will be handled in a coded manner and your personal information cannot be recognized in the study results, statements, or publications.

Only personal information essential for the purpose of the study will be entered in the study register. Your name, personal identification number, and contact information will be stored separately from other study data and will not be given to the sponsor of the study. In the results and other documents, you will only be referred to by an identification code that does not reveal your identity. The register will be stored at the study site for as long as required by the regulations concerning investigational products and marketing authorizations.

Information regarding the state of your health, which are relevant for the study, can be collected from other Health Care Units. The investigator can find the necessary information based on your personal identity number. In Finland the regulatory authority (Finnish Medicines Agency Fimea) has the right to assure that the study data are acquired and the study is conducted properly. Also, foreign authorities and representatives of the sponsor have the right to conduct audits. In these cases, the data are handled under the supervision and the responsibility of the investigator. The data may also be disclosed to regulatory authorities for a marketing approval application and safety assessment. In any case your personal information will be handled confidentially.

If you decide to withdraw your consent the information and samples obtained until your withdrawal will be used as a part of the study data. This is essential to confirm the study results.
Your coded information may also be disclosed to another investigator or, for example after a business acquisition, to another sponsor. Also, in this case all parties are required to maintain complete confidentiality. The data are not disclosed to other parties such as insurance companies.

The study results will be published in a coded manner in a public international database:
https://register.clinicaltrials.gov/

Cost of the study and financial statements
The study product and procedures related to the study are free of charge to you. Your loss of earnings and your travel costs due to the study visits will be compensated based on actual costs as evidenced by receipts.

Herantis Pharma is responsible for financing the study and for remunerating the study sites for implementing the study. The investigators and other personnel engaged in the study are paid a separate compensation for conducting the study.

Insurance for the subjects

If the investigational product or a procedure related to the study causes a personal injury, you can apply for a compensation.

Compensation for harm caused by the investigational product is applied from the Finnish Co-operative for Pharmaceutical Injury Indemnities whose member Herantis Pharma is. The pharmaceutical insurance of the co-operative compensates the unexpected side effects caused by the study product in accordance with the policies that are more specifically described in the insurance terms and conditions.

For harm caused by other reasons than the investigational product, a compensation is applied from the Patient Insurance Center that manages the handling of compensations regarding patient injuries. The patient insurance compensates for personal injuries that are caused during health care and medical care in compliance with the Patient Injury Act (PIA) and in accordance with the policies that are more specifically described in the PIA.

Termination of the study

The investigator will discuss your treatment with you after the termination of the study.

The investigator or the sponsor may have to discontinue your participation prematurely. In this case, the investigator will discuss the procedures regarding the termination with you.

Additional information

If you have any questions about the study, please contact the investigator or other personnel involved in the study. You may discuss with them about the side effects or unusual symptoms you may have experienced, and any other issues you may have on your mind.

Contact information:

x hospital
x street x
xxxxx city

Investigator/study nurse _____is available during the study by phone at _____ or _____.

You will receive a copy of the information leaflet and the consent form.
Please retain this information leaflet and the consent form.

Annex 1: Study schedule

CONSENT FORM

I have been invited to participate in a clinical study sponsored by Herantis Pharma Plc that is conducted with the investigational gene therapy product Lymfactin®; EudraCT number 2017-004443-20.

I have read the aforementioned statement (information leaflet version 1.0, 01.10.2018) and received enough information on the study and the study-related collection, handling, and disclosure of data. The study content has also been explained to me orally and I have received a sufficient answer to all my study-related questions. The information and statements were told by _____ , ___/___/ 20__ . I have had enough time to consider my participation in the study.

I understand that my participation in this study is entirely voluntary. I have the right to discontinue the study and withdraw my consent without providing any reason at any point of the study. Declination, discontinuation or withdrawal of consent from the study does not affect the continuation of my treatment, my status as a health care customer or cause me other negative consequences. I am aware that the information collected from me before my discontinuation or withdrawal of consent will be used as a part of the study data and the safety assessment of the investigational product.

With my signature I confirm that I will participate in the study described and referred to in this document and I consent voluntarily to participate as a study subject in this study. I allow that information regarding my health can be obtained from other Health Care Units, if it is necessary for the study. I consent to the handling of my personal information in case of an audit by a foreign authority and a quality control procedure conducted by a representative of the sponsor.

_____ _____

Signature Date

_____ _____

Print name Birth date or personal identification number

_____

Street address

Consent received

_____ _____

Signature of the investigator Date

_____

Print name

The original signed document will be stored in the archive of the investigator and a copy will be given to the subject.

SCHEDULE FOR THE STUDY:

A Phase II, double-blind, placebo-controlled, randomized study to assess the efficacy, safety and tolerability of Lymfactin® (AdAptVEGF-C Adenoviral Vector) in combination with a surgical lymph node transfer for the treatment of patients with secondary lymphedema associated with the treatment of breast cancer.

	Visit 1A screening	**Visit 1B screening**	**Visit 1C screening**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11A**	**Visit 11B**	**Visit 12A**	**Visit 12B**	**Follow-up Visits**
	90-30 days pre-op	Within 45 days pre-op	14 days from Visit 1B	1 day pre-op or the day of the op	1 day post-op	Discharge 7 ± 2 days post-op	30 ± 5 days post-op	60 ± 5 days post-op	90 ± 10 days post-op	120 ± 10 days post-op	150 ± 10 days post-op	180 ± 14 days post-op	360 ± 14 days post-op	14 days from Visit 11A	720 ± 14 days post-op	14 days from Visit 12A	3 and 5 years post-op
Informed consent	x																
Medical history (breast cancer and lymphedema)	x																x
Demographic data	x																
Medical examination	x			x		x	x		x			x	x		x		
Height	x																
Weight	x			x		x	x		x			x	x		x		
Blood and urine tests, wound secretion	x			x	x	x	x		x			x	x		x		x
Pregnancy test	x			x		x	x	x	x	x	x	x					
Blood pressure and body temperature	x			x	x	x	x		x			x	x				
ECG	x			x		x	x						x				
Lymphedema related measurements	x	x							x			x	x	x	x		
Lymphoscintigraphy		x												x	x		
Quality of life assessment		x							x			x	x		x		
PET CT or CT of the chest and abdomen		x[1]												x[1]			x
MRI lymphangiography (optional)[2]			x										x			x	
Surgical lymph node transfer and administration of study product				x													

[1]The computed tomography (CT) of the chest and abdomen is conducted one day before or after the lymphoscintigraphy measurement.
[2] The MRI lymphangiography, and therefore the Visit 1C, is optional and subject to the Principal Investigator's decision; however, if a patient's baseline MRI lymphangiography is done at Visit 1C then it is also required at Visit 11A and 12B.

In addition, you are requested to record any other medication you are using and possible adverse events during the entire study, in the study diary you will receive. Your notes in the diary will be reviewed during the study visits.