

Recombinant Advisory Committee Meeting OBA Protocol 1190

Lymfactin™ (LX-1101) for Laurantis Pharma Ltd

5th December 2012

LYMFACTIN™ (LX-1101)

- **Clinical Indication:**

- Lymfactin (LX-1101, VEGF-C Gene in an adenoviral vector) is under development for the treatment of patients with secondary lymphedema associated with the treatment of breast cancer.
- Therapy with Lymfactin will involve a surgical operation – a lymph node with associated adipose flap will be harvested from the patient's lower abdominal wall, injected via a Perinodal route with Lymfactin, and then transferred to the axillary region.

Therapy with Lymfactin aims to reinstate a functional lymphatic system.

Breast Cancer Associated Lymphedema



Patient shown shortly after mastectomy



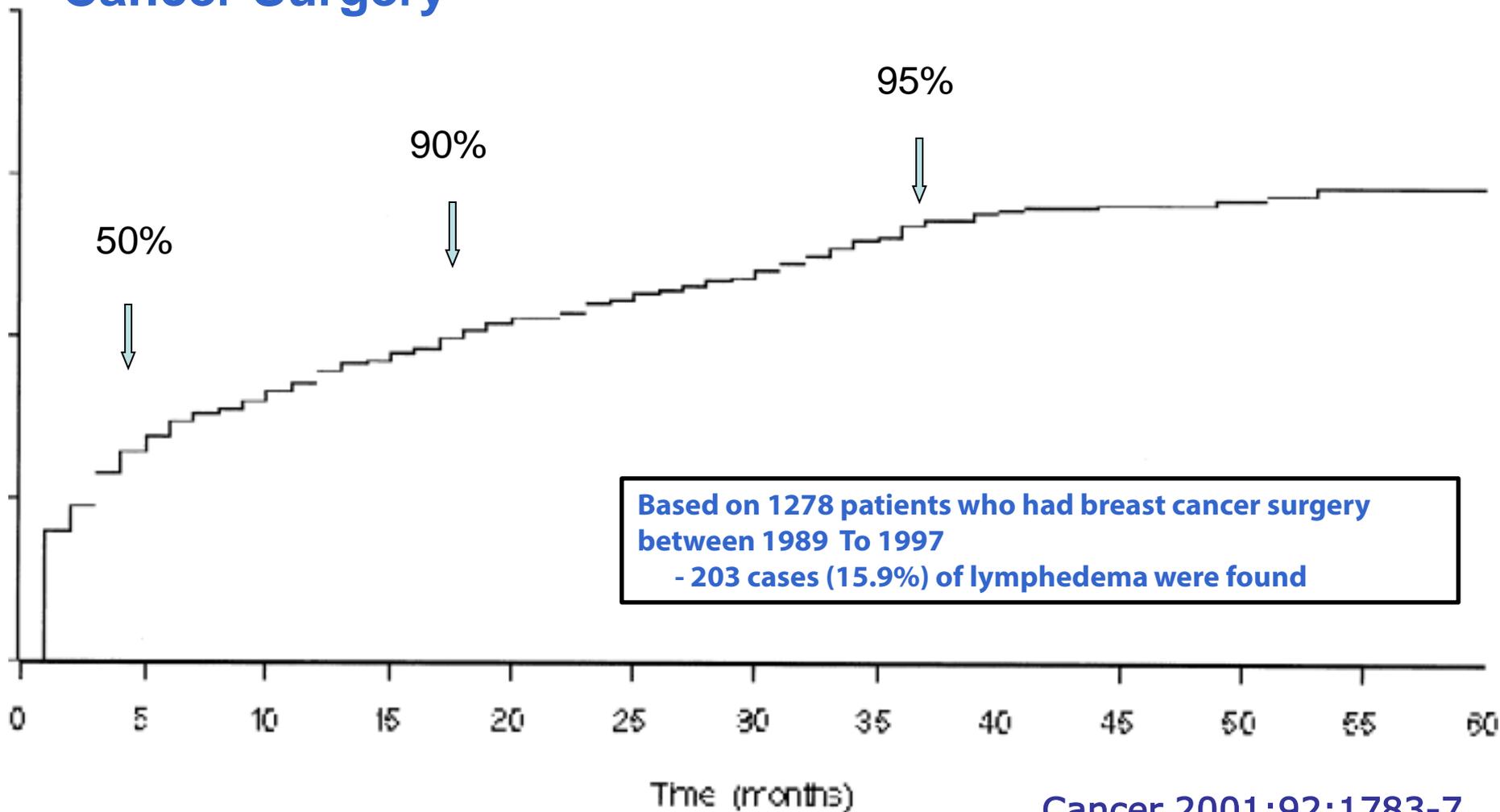
Patient following development of lymphedema



- **Lymphedema is a chronic, progressive swelling of the affected tissues caused by dysfunction of the lymphatic vasculature**
- **Breast cancer surgery, especially axillary lymph node dissection, damages lymphatic vasculature causing lymphedema**
- **Incidence: Around 15,000 new breast cancer associated lymphedema patients in the U.S. each year.**
- **There is no cure or satisfactory treatment for lymphedema**

Lymphedema is a disabling, disfiguring and debilitating condition severely affecting a patient's quality of life.

Cumulative Incidences of Lymphedema after Breast Cancer Surgery



Cancer 2001;92:1783-7

Lymphedema – Assessment of Disease Status

Clinical Signs & Symptoms	Assessment Method
Progressive accumulation of extracellular fluid in the arm	Bio-impedance Spectroscopy (Sensitive to detect the pre-disease conditions)
Progressive increase in total limb volume	Limb volume truncated cone approximation method based on limb circumference (Limb ratios determination)
Progressive fibrosis of cutaneous & subcutaneous tissues	Skin callipers
Impact & effects on psycho-social status and activities of daily living	Use of quantifiable Quality of Life Instruments

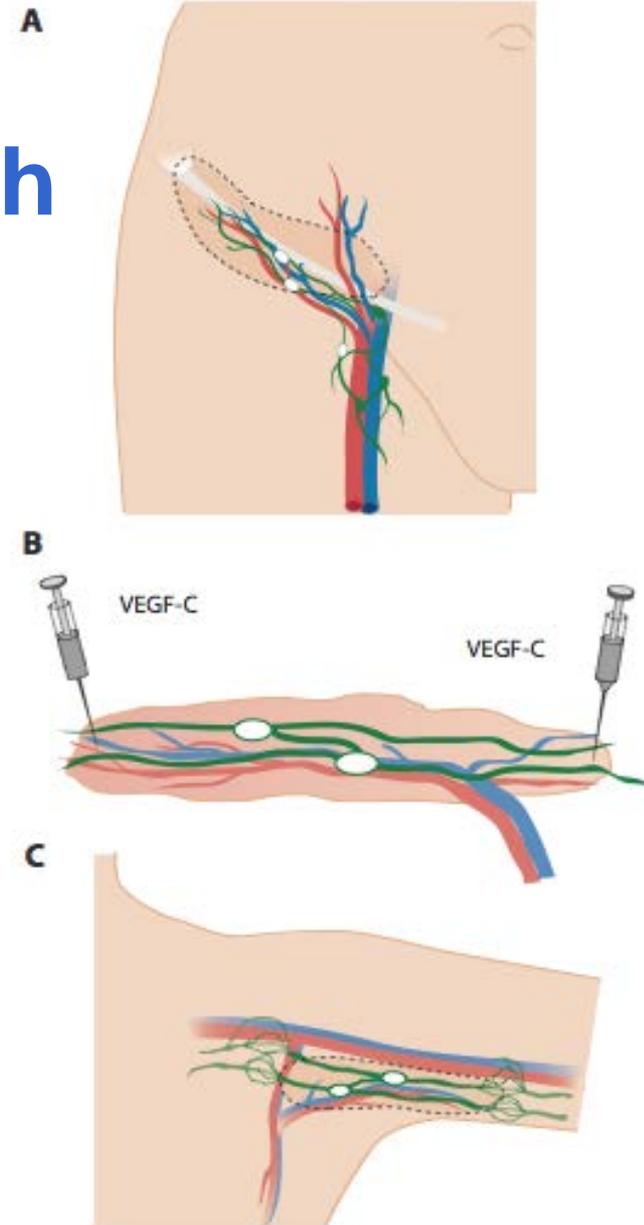
Breast Cancer Associated Lymphedema

Current Treatment Approaches

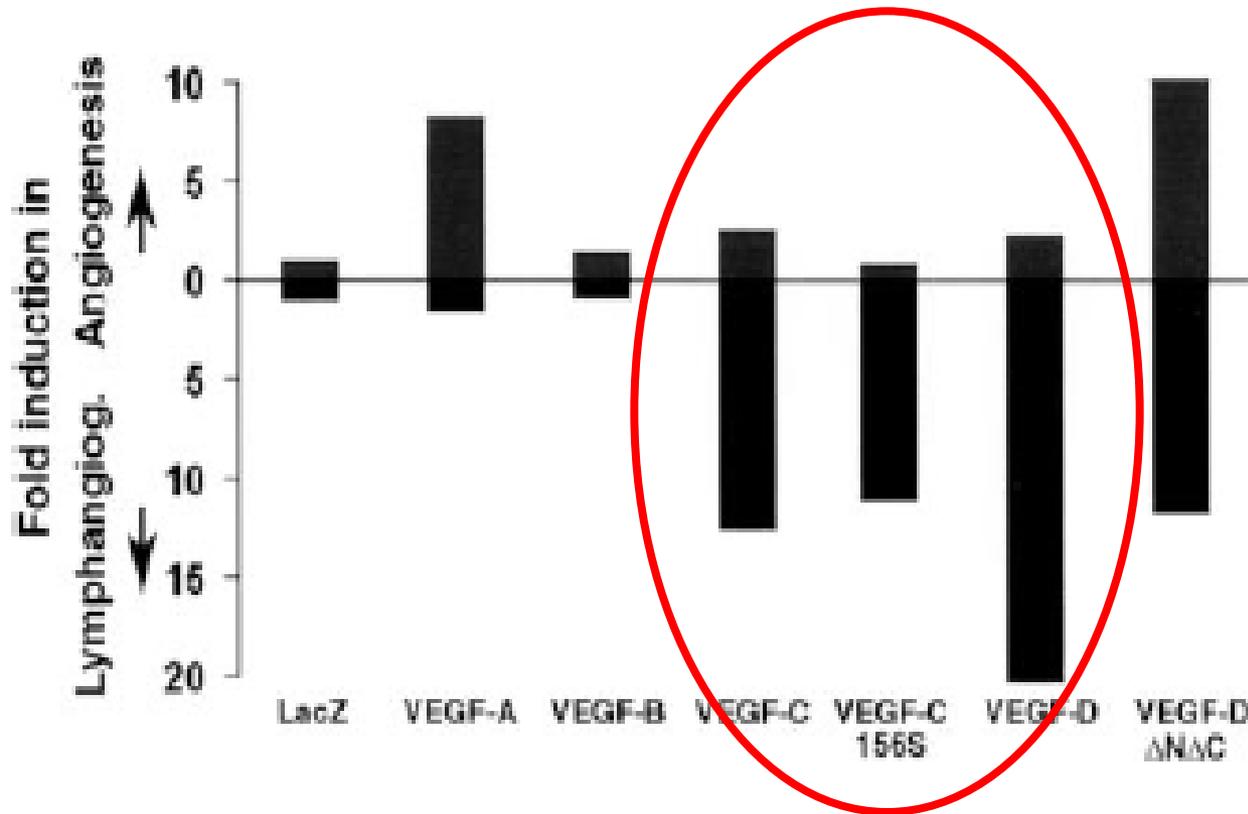
- **Physical therapy**
 - Physiotherapy.
 - Manual lymph drainage
 - Multilayer bandaging
 - Pneumatic compression therapy
 - Exercise
- **Drug therapy**
 - Diuretics are a commonly used treatment, but there is no evidence that they bring any clinical benefit
- **Surgery**
 - Removal of excess tissue (reducing/debulking operations or liposuction) followed by continued compression therapy, such as hosiery
 - Lymphatic-Venous anastomosis practiced, but efficacy is questionable
 - Lymph Node Transplantation also performed, but with low success rate at approximately 20-30%

Lymfactin – Therapeutic Approach

Combining:
Microvascular
lymph node transfer and
lymphangiogenic
growth factors

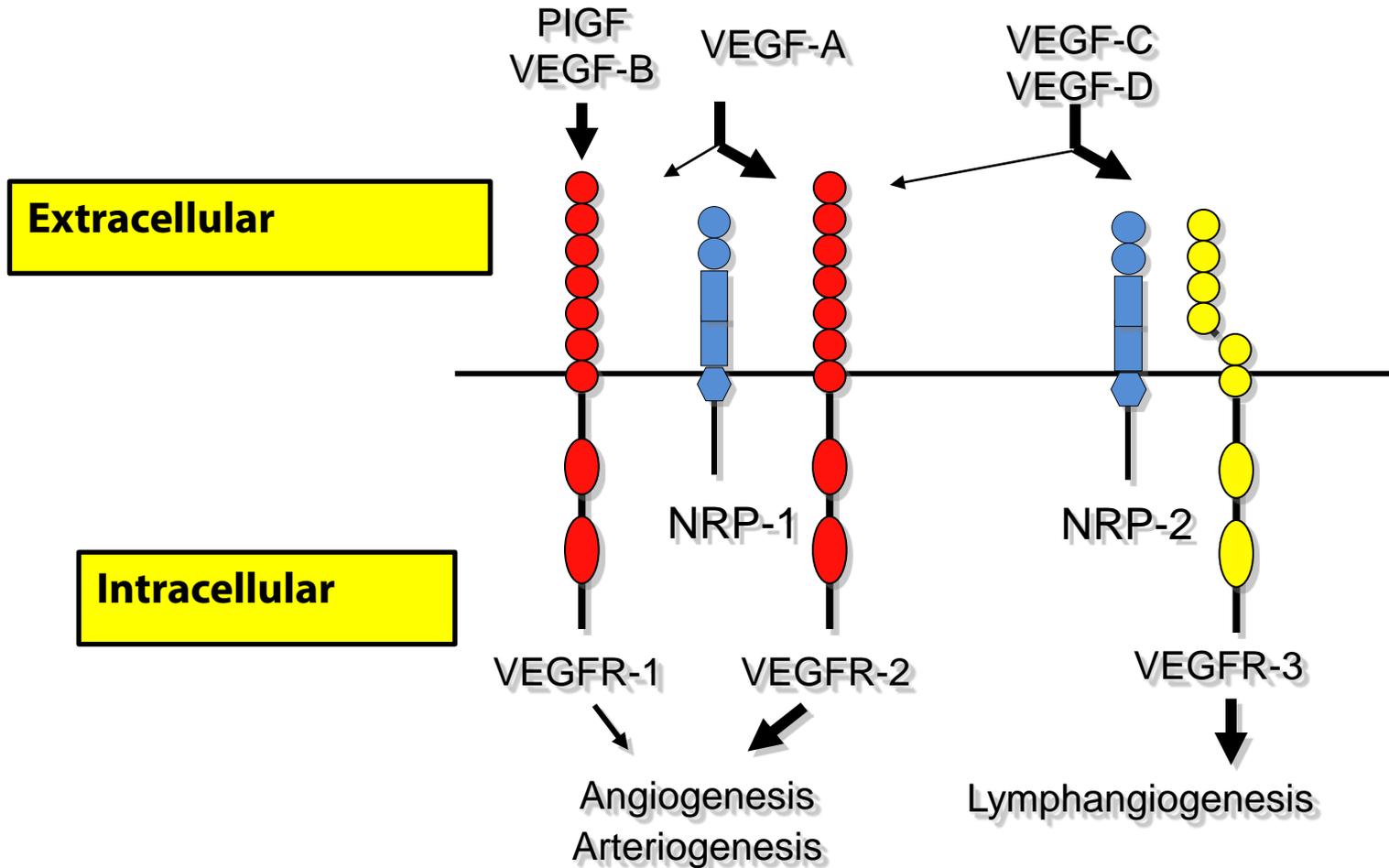


VEGF-C and -D Promote Lymphangiogenesis in Rabbits



Rissanen et al. *Circ Res* 2003

Vascular Growth Factors and Receptors



Veikkola et al *EMBO J* 2001

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Animal Models

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Proof-of-Concept in Mice and Pigs

Animal models of Lymphedema -Limitations

- No experimental lymphedema model that truly reflects the human situation
- Other mammals do not develop clinical lymphedema
 - Experimental models have significant surgical morbidity out of proportion to human counterpart
 - Animal have greater regenerative capacity of lymphatic system than humans
- Lymphatic anatomical differences in animals & humans

Proof-of-Concept Studies in Mice and Pigs

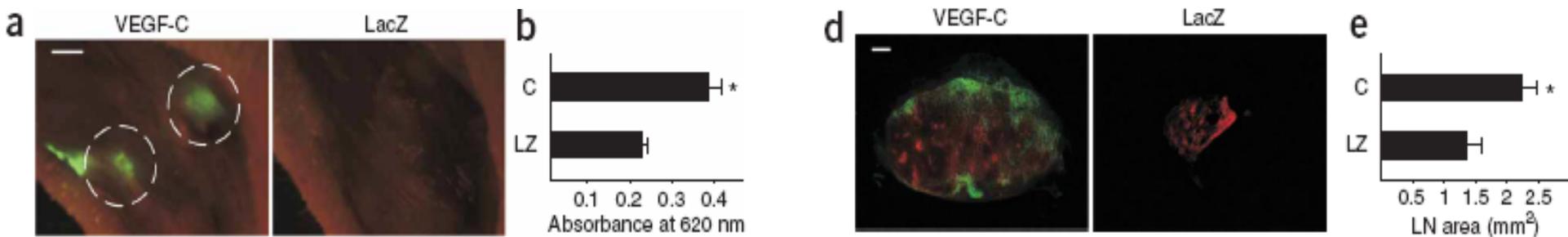
- Initial pharmacology effects assessed in mouse model using axillary lymph node dissection & allogeneic lymph node transfer with/without VEGF gene administration
- Due to limitations in size of mice a larger animal model was needed closer to humans to:
 - Investigate development and growth of lymphatic vasculature over a greater surface area
 - Confirm the most appropriate VEGF gene ligand to use
 - VEGF-C vs. VEGF-D
 - Determine the optimum route of gene product administration
 - Intranodal vs. Perinodal
- Doses used – Mice – predominately 5×10^{10} vp
 - Pigs - predominately 1×10^{11} vp

LYMFACTIN - Proof-of-Concept

Mice – Transplanted Lymph Nodes

Function at 2 months

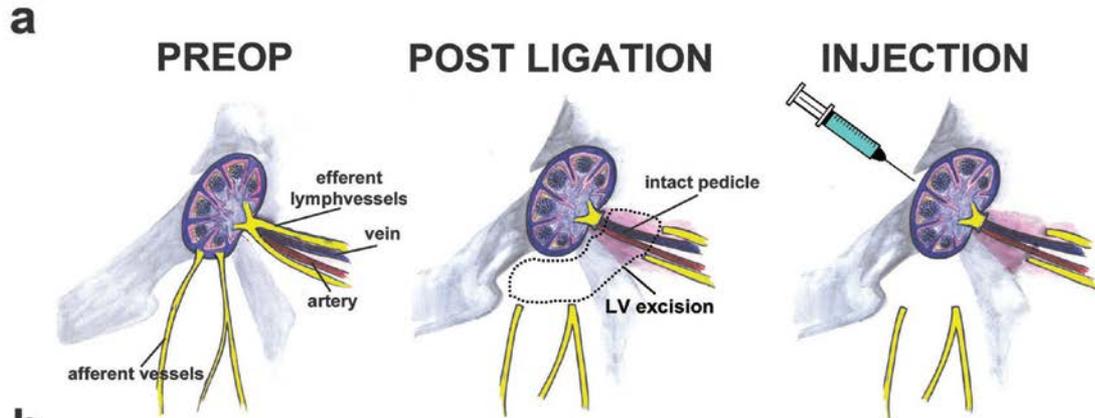
Size at 2 months



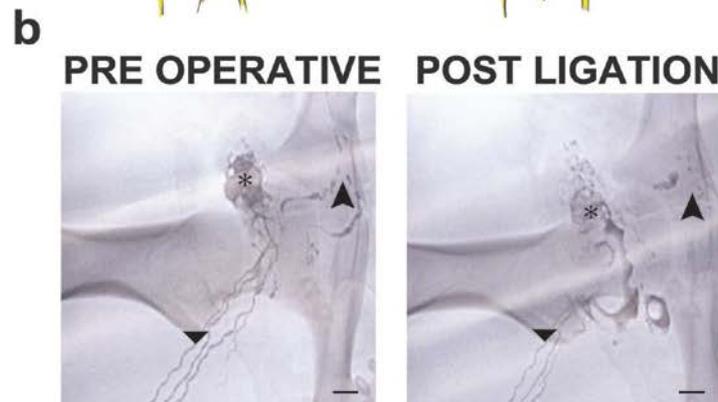
- VEGF-C increased lymph node transplantation success rate from 22% to 82% with increased afferent & efferent lymphatic connections with the host lymphatic vasculature
- VEGF-C improved lymphatic drainage considerably
- VEGF-C treated lymph nodes were larger & did not regress

Tammela et al *Nature Med* 2007

Pig Lymphedema Model to Evaluate the Effects of VEGF Therapy



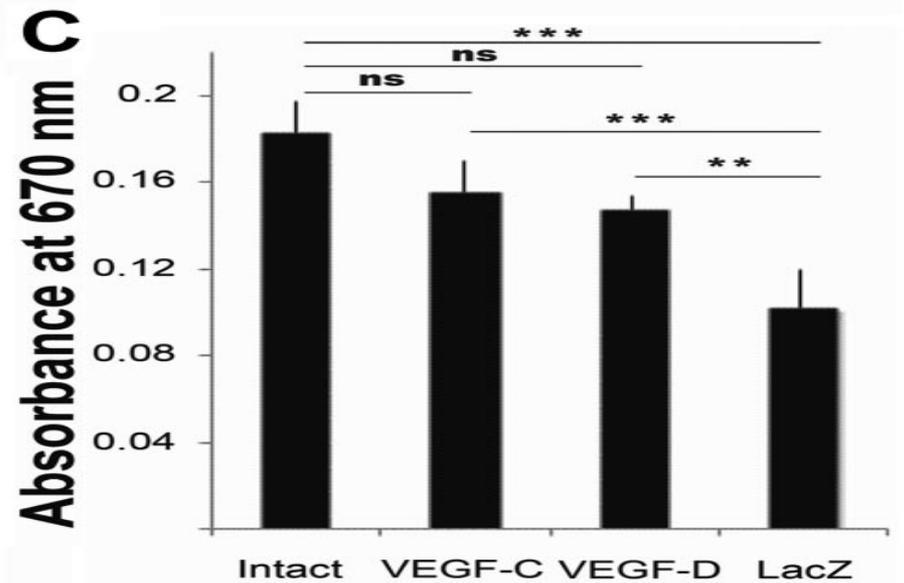
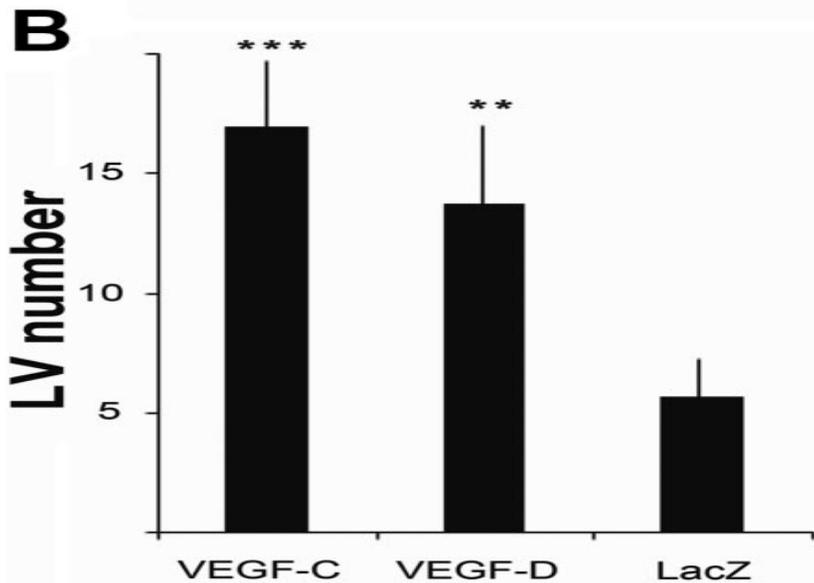
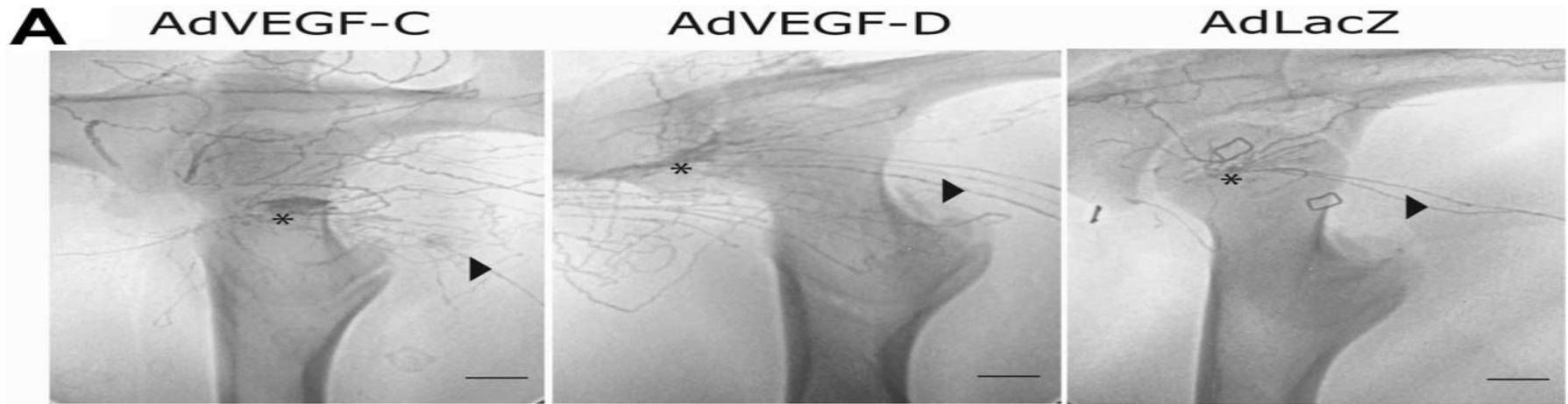
Removal of afferent and efferent lymph vessels, lymph node sutured down & followed by adenoviral VEGF-C/D gene therapy



Perioperative lymphangiography before and after the lymph vessel excision

Lähtenvuo et al. *Circulation*, 2011

LX-1101 - Proof-of-Concept in Pigs



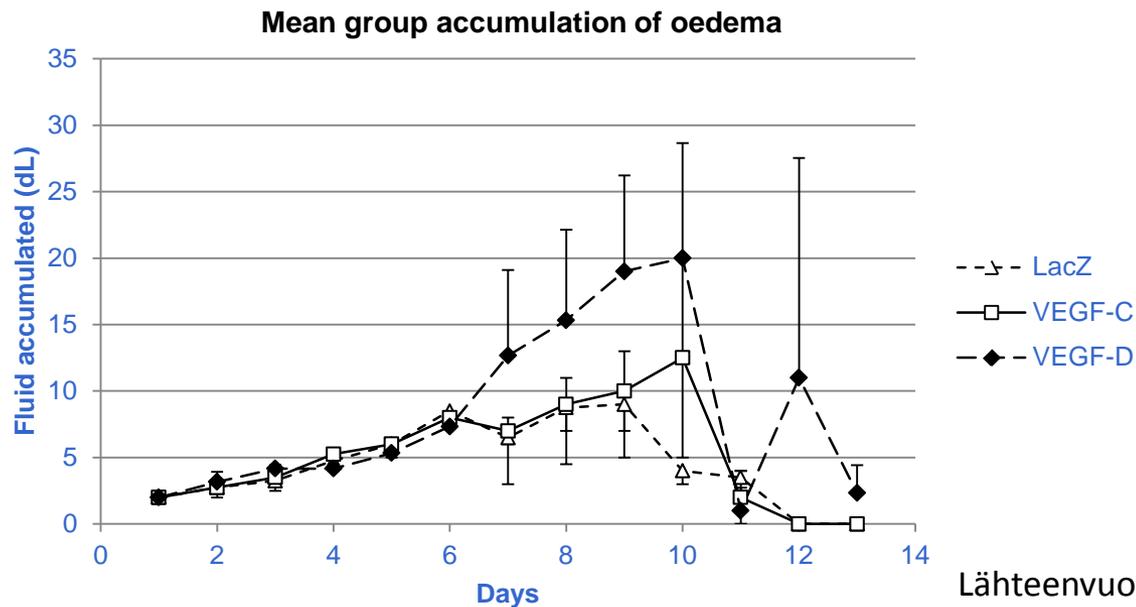
Pig Lymphedema Model to Evaluate the Effects of VEGF Therapy: Results

Both VEGF-C and VEGF-D

- Increased the number and size of lymph vessels more than LacZ vector

VEGF-C was better in

- Preventing seroma fluid accumulation at the surgical site

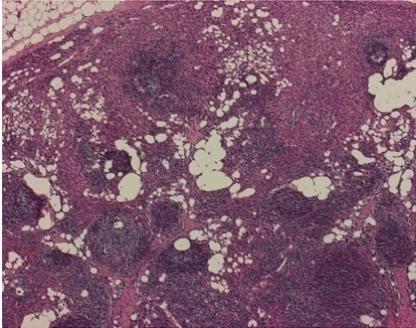


Lähtenvuo et al. *Circulation*, 2011

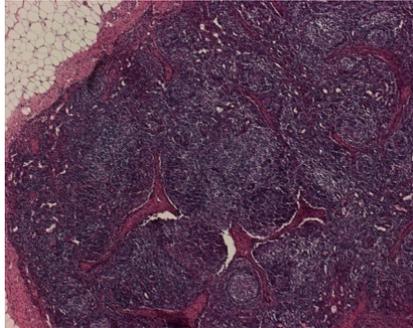
Lymph Node Transplantation with VEGF-C & -D in Pigs

Eosin-staining of the lymph nodes 2 months postoperatively

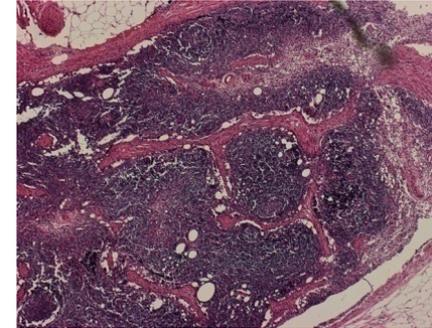
LacZ



VEGF-C



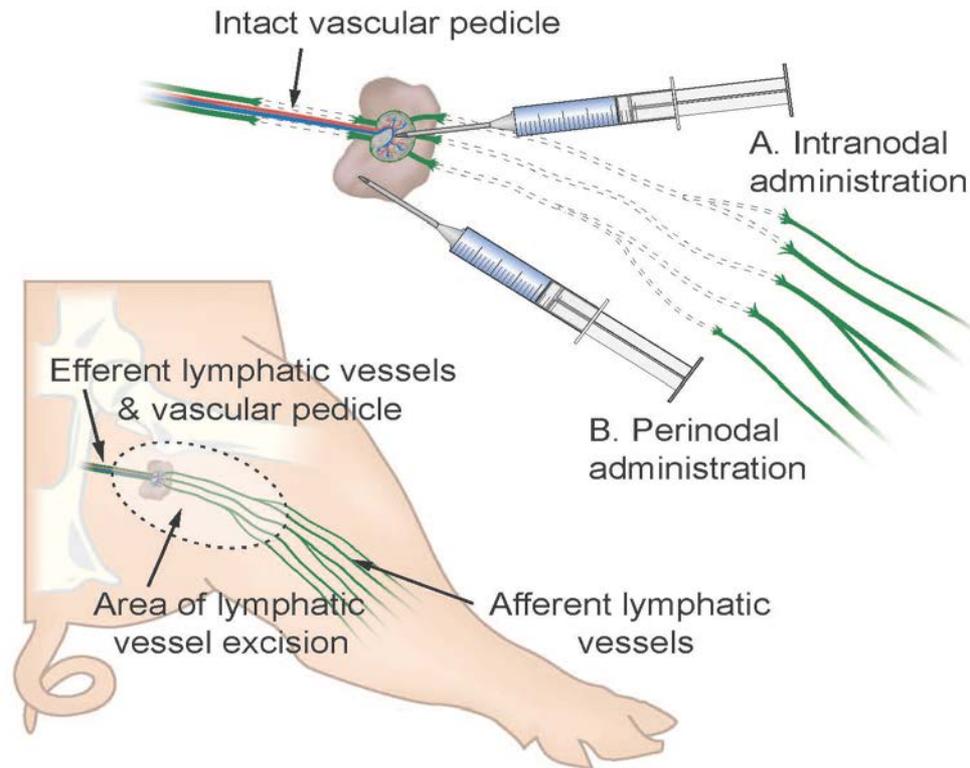
VEGF-D



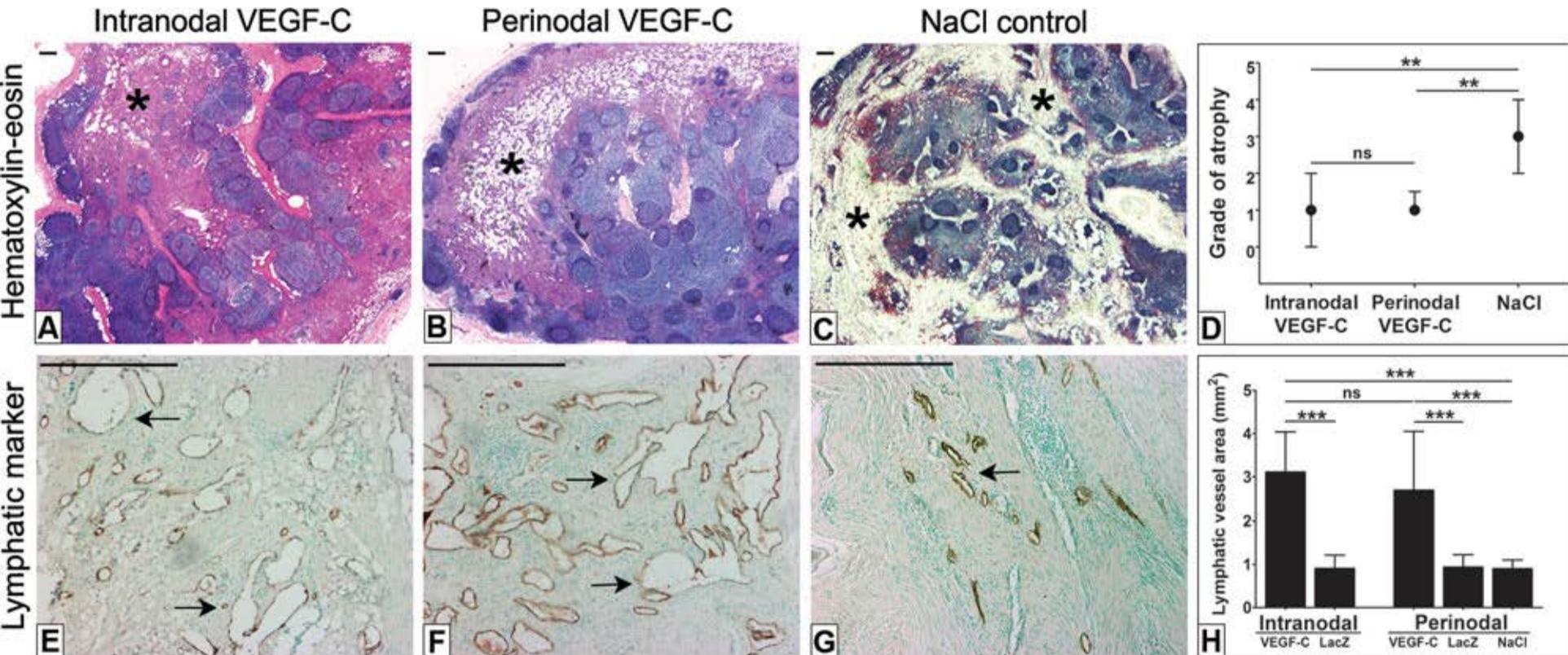
- In the control treated animals, the follicular structure was in many areas replaced by fibrous and fat tissue.
- In the VEGF-D treated animals, lymph nodes revealed signs of edema in many areas.
- The follicular structure of lymph nodes was best preserved in the VEGF-C treated animals.

Lahtenvuo M et al *Circulation* 2011

Pig Lymphedema Model to Evaluate the Effects of VEGF Therapy by Intranodal or Perinodal Injection



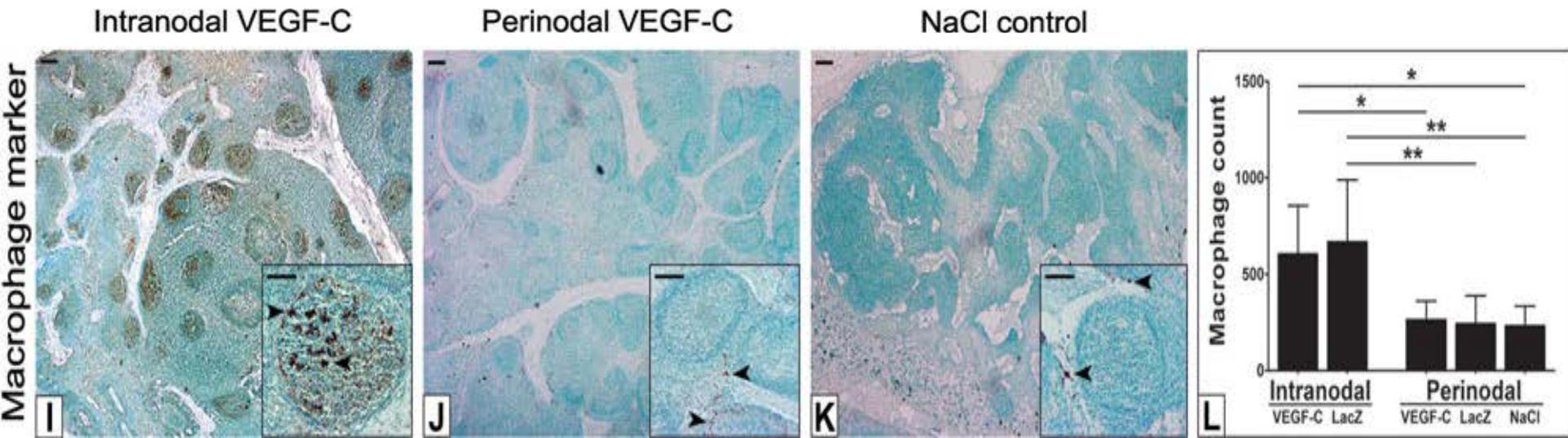
Effects of VEGF Therapy by Intranodal or Perinodal Injection



* atrophied areas → lymphangiogenic effect in the VEGFC- transduced animals

Honkonen et al *Ann Surgery* 2012

Effects of VEGF Therapy by Intranodal or Perinodal Injection



Proof-of-Concept Studies in Mice and Pigs

Summary of Results

Mouse Studies:

- VEGF-C increased lymph node transplantation success rate from 22% to 82% with increased afferent & efferent lymphatic connections with the host lymphatic vasculature
- VEGF-C improved lymphatic drainage considerably
- VEGF-C treated lymph nodes were larger & did not regress

Pig Studies:

- Growth of lymphatic vasculature can be achieved over a large surface area
- VEGF-C is the most appropriate VEGF gene ligand to use
- The Perinodal route of administration is the optimum route to use

LYMFACTIN (LX-1101)
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Toxicology & Biodistribution Study

LYMFACTIN - Toxicology & Biodistribution Study

- **Study objective:**

- To assess the toxicity and biodistribution of AdAptVEGF-C after either single i.v. administration or perinodal fat injection in the pig

- **Study Design:**

- Large Domestic Pigs – Single dose administration
- Lymph-node Transfer plus either
 - Perinodal Injection of Lx-1101
 - Intravenous Injection of Lymfactin
 - Controls – Formulation Buffer or LacZ gene
- 3 dose levels LX-1101 – 1×10^{10} , 1×10^{11} , 1×10^{12} vp.
- Duration of observation up to 60 days (3, 30 & 60 days)
- Animal Numbers – 70 animals (males & females)

LX-1101 - Summary of Toxicology & Biodistribution Results

- **Pathology**

- Macroscopic examination performed 3, 30 and 60 days after treatment showed no treatment-related findings
- Microscopic examination of organs and tissues collected showed no treatment-related findings

- **Hematology and clinical chemistry**

- No significant treatment-related effects

- **Biodistribution/qPCR analysis**

- In i.v. treated group - AdVEGF-C was detected in the liver, lung and spleen
- In perinodal injection treated group - AdVEGF-C was found only in the target and draining lymph nodes, but the signal was not present at day 60

- **Adenoviral Antibodies and VEGF-C Expression**

- Analysis underway

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Clinical Development

LYMFACTIN – Clinical Protocol

- **A Phase I Open–Label Study to Assess the Safety, Tolerability and Preliminary Efficacy of Lymfactin, (VEGF-C Adenoviral Vector) in the Treatment of Patients with Secondary Lymphedema Associated with the Treatment of Breast Cancer**
- **Study Design**
 - Dose Escalation
 - 3 Cohorts - 1×10^9 vp, 1×10^{10} vp & 1×10^{11} vp
 - 3+3 Patients per cohort to establish the Optimum Tolerated Dose (OTD)
 - Dose Expansion at OTD
 - up to 24 Patients in total to be treated

LYMFACTIN – Clinical Protocol

- **Objectives of Study:**
 - Primary:
 - Evaluate safety and tolerability of Lymfactin
 - Secondary:
 - Establish appropriate dose of Lymfactin for use in future studies
 - Determine the pharmacokinetics (biodistribution) of a single dose of Lymfactin
 - Assess the preliminary efficacy of Lymfactin in the treatment of secondary lymphodema associated with the treatment of breast cancer

LYMFACTIN – Clinical Protocol

• Phase I Clinical Study – Patient Population

Adult female patients (aged 18-70 yrs) with secondary lymphedema in the arm associated with breast cancer who:

- Have undergone removal of their lymph nodes in the axilla on the affected side of their breast cancer
- Have undergone prior radiotherapy
- Require garment use as compression treatment for their lymphedema in the affected arm
- Have their affected arm that is greater than 10% larger than their unaffected arm
- Have the presence of pitting edema in the affected arm

In the USA, the procedure will not be performed at the same time as breast reconstruction

LYMFACTIN – Clinical Protocol

- **Phase I Clinical Study – Patient Population**

- **Criteria to Minimise Risk in Breast Cancer Patients**

At Screening:

- Patient selection in close collaboration with the oncologists
- No evidence of recurrent or active breast cancer in the past 2 years
- CT scan of chest & abdomen to be performed at screening

Exclusion Criteria:

- >3 positive axillary lymph nodes
- Extracapsular nodal extension (local invasion)
- Stage III disease (significant prognostic factor in breast cancer)
- Inflammatory (T4) breast cancer
- Invasive micropapillary breast carcinoma
- Patients with high risk of recurrence based on multi-gene signatures
- Metastatic (Stage IV) breast cancer

LYMFACTIN – Clinical Protocol

VEGF-C - Minimising Risk in Breast Cancer Patients

Theoretical Considerations:

- Adenoviral VEGF-C expression lasts only for about one-to-two weeks
- Breast reconstruction alone induces tissue hypoxia, VEGF-A (angiogenesis), VEGF-C and other cytokines
- Lymph nodes produce VEGF-C (lifelong); lymph node transfer is already been used in the treatment of breast cancer related lymphedema
- In tumors, VEGFs are expressed by the cancerous cells, here VEGF-C is produced by cells in the lymphatic tissue flap (injected into normal donor tissue)
- VEGF-C couples lymph node function to the draining lymph node vessels

LYMFACTIN – Clinical Protocol

• Phase I Clinical Study – Assessments

1. Safety and Tolerability

- Clinically significant Adverse Events including those related to wound healing will be included
- Physical examination & vital signs
- 12-lead electrocardiogram (EKG)
- Laboratory tests including clinical chemistry, hematology and urinalysis.
- Characterization of the virus biodistribution of LX-1101 out to 90 days.
- Presence and titer of neutralizing antibodies to the adenoviral vector to 6 months.

- Toxicity will be graded by the Investigator according to the NCI criteria (CTCAE V4.03).
- Dose Limiting Toxicities will also be considered in relation to Cohort dose escalation

LYMFACTIN – Clinical Protocol

- **Phase I Clinical Study – Assessments**

- 2. **Efficacy measures to assess the effect of the intervention with LX-1101:**

- Reduction in volume of the affected limb at baseline, 1, 3, 6 and 12 months. (Modified Frustrum Measurements)
- Extracellular water content (bio-impedance ratios measurements) at baseline, 1, 3, 6, and 12 months
- Quality of Life – patient assessment by use of the Lymphedema Quality of Life Inventory & SF-36 questionnaires at baseline, 1, 3, 6, and 12 months.

Points raised in relation to the Informed Consent Document

- The final Informed Consent Document will be written to correspond with the final Clinical Study Protocol
- All risks relating to the surgical procedure & risks in relation to the use of Lymfactin (LX-1101) will be provided in the Informed Consent Document

Lymfactin™ (LX-1101): Development of a treatment for patients with secondary lymphedema associated with breast cancer

Summary

- Currently there is no cure or satisfactory treatment for lymphedema.
- Lymfactin (VEGF-C Gene in an adenoviral vector) has been able to reconstitute a functional lymphatic system in animal models
- The preclinical toxicology and biodistribution study demonstrated that Lymfactin was safe and well tolerated, with very limited biodistribution confined to the site of administration.
- A Phase I clinical study in patients with secondary lymphedema associated with breast cancer will be initiated during 2013
- Lymfactin has the potential to become the first disease-modifying therapy for secondary lymphedema



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