LE&RN Online Symposium:

# Clinical Progress With Lymfactin©: Could Gene Therapy Cure Lymphedema?

Presented by Pekka Simula, CEO, Herantis Pharma Plc

Lymphatic Education & Research Network

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# LE&RN Online Symposium 13 June 2018

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# Disclosures

- Human clinical studies presented here have been conducted under the approvals of Finnish Medicines Agency Fimea, Ethics Committee, the Board of Gene Technology of Finland, and other appropriate bodies, in compliance with applicable rules and regulations
- Preclinical studies presented here have been conducted under appropriate ethical permissions and in compliance with applicable rules and regulations.

# Herantis Pharma Plc (HRTIS:FH)

- Herantis is a public drug development company advancing **two highly-differentiated clinical assets for unique market opportunities**
  - **Lymfactin® gene therapy for secondary lymphedema**
  - **CDNF therapy for Parkinson's Disease**, with potential in treating other neurodegenerative diseases
- Both programs originate from scientific discoveries made by **world-leading researchers** at the University of Helsinki
- Clinical success will be based on **company's deep development expertise**

We develop regenerative medicine based on cutting edge science, for patients in need.

HRTIS
Nasdaq
First North listed

# Lymphedema: Significant and growing unmet need

"The psychosocial impact of lymphedema has been described to be as distressing as the initial diagnosis of Breast Cancer."
– Shih et al., J Clin Oncol 2009

# Secondary lymphedema
## Disease, Market and Awareness

- **Lymphedema (LE)** is a chronic, progressive swelling of tissues caused by the dysfunction of the lymphatic vasculature
  - Lymphatic system is unable to return interstitial fluid to bloodstream
  - Estimated **140 million people** worldwide have LE; there is no cure
  - Estimated treatment cost **$10,000 per year** in the USA
- **Secondary lymphedema** is caused by e.g. disease, trauma, or surgery
  - **Disabling and disfiguring disease**, which severely affects quality of life
- **Herantis collaborates with international LE advocacy LE&RN** (Lymphatic Education & Research Network)
- **Lymphedema awareness is increasing:**
  - Hollywood superstar, lymphedema advocate **Kathy Bates is a strong and visible LE spokesperson**

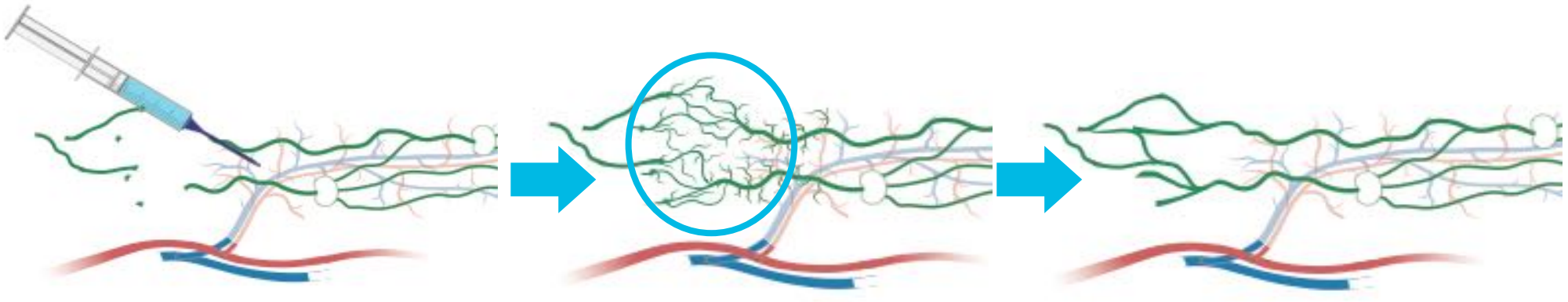
# Lymfactin® gene therapy: Scientific background

# What creates our lymphatic vessels?

- The formation of lymphatic vessels is called **lymphangiogenesis**
- Lymphangiogenesis is promoted by a protein called **VEGF-C**: A natural growth factor, which we all have
- Thus the damages of the lymphatic system could be repaired by increasing the VEGF-C levels. Unfortunately, just injecting the VEGF-C protein would not maintain high enough VEGF-C levels for a long enough time in the damaged area

# Lymfactin® gene therapy
## aims to cure the underlying cause of secondary lymphedema

- Lymfactin® is a **gene transfer vector** carrying the human VEGF-C gene
- Lymfactin® instructs the patient's own cells to produce VEGF-C in the damaged area where Lymfactin® is administered
- Single-dose treatment with **local and transient VEGF-C expression** for about two weeks

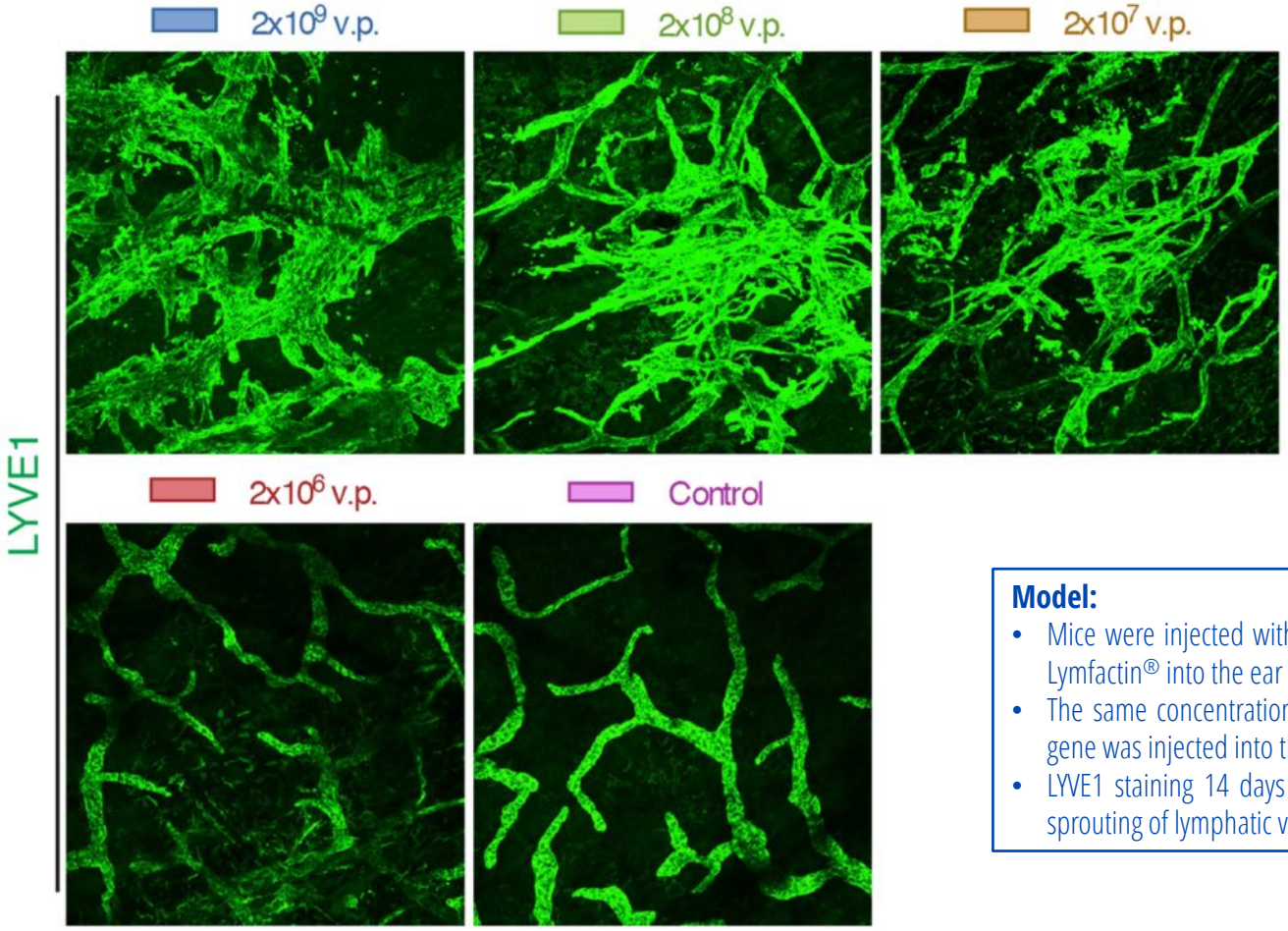


1. Lymfactin® injection

2. VEGF-C expression in the damaged tissue ➔ lymphangiogenesis

3. Functional lymphatic network

# Clear dose response in lymph vessel sprouting following Lymfactin® administration in mice ear skin



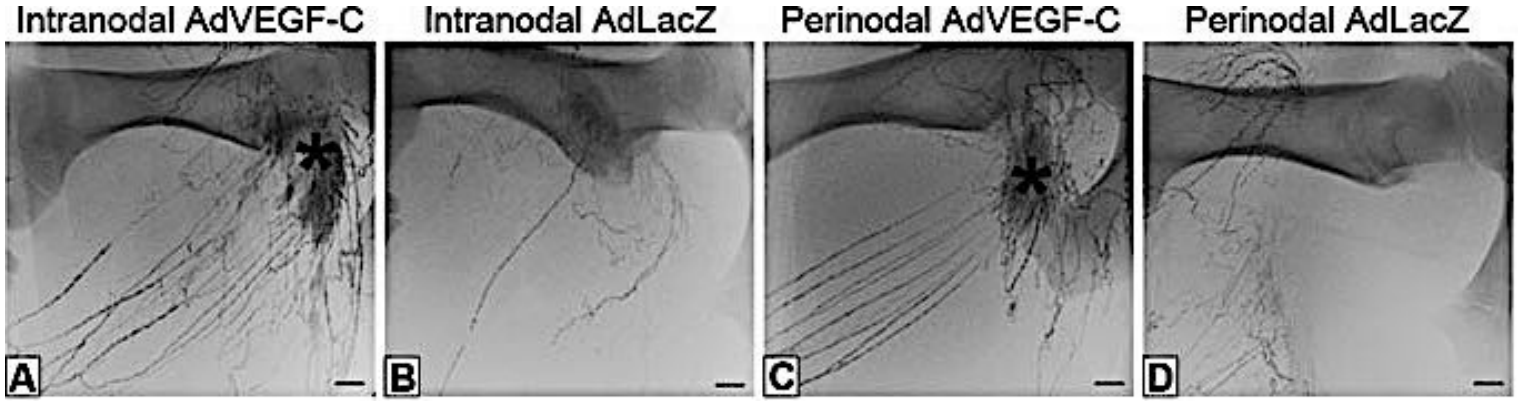

**Model:**

- Mice were injected with 2 x $10^6$ to 2 x $10^9$ viral particles of Lymfactin® into the ear skin.
- The same concentration of a control vector coding for LacZ gene was injected into the contralateral side
- LYVE1 staining 14 days after virus administration reflecting sprouting of lymphatic vessles

Unpublished data

# Perinodally administered Lymfactin® efficiently improves lymphatic vessel regeneration and lymph node function in a porcine model

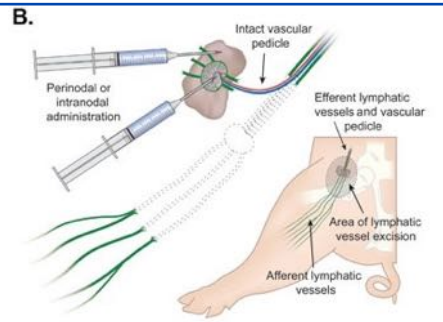
## Native lymphangiogram taken 2 months after the lymph node transfer:




| | | | | |
|---|---|---|---|---|
| **Total no of lymphatic vessels** | 12.5±4.8 | 5.9±1.5 | **13.7±4.0** | 5.8±5.5 |
| **Lymphatic vessels connected** | 9.1±6.7 | 1.0±1.7 | **9.9±4.9** | 2.8±3.4 |
| **Size of lymph node (cm³)** | 29.9±7.4 | 12.0±5.9 | **27.7±12.4** | 11.5±4.7 |

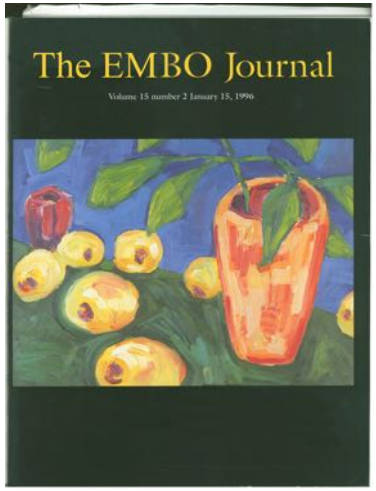
**Model**

- Porcine lymphedema model mimicking lymph node transfer in human lymphedema patients.
- Lymphatic vasculature was destroyed by excising all afferent lymphatic vessels and all efferent lymphatic vessels from 5 cm and 3 cm radius, respectively, surrounding the lymph node.
- Virus carrying either VEGF-C or LacZ gene was injected subcapsularly into the exposed lymph nodes.



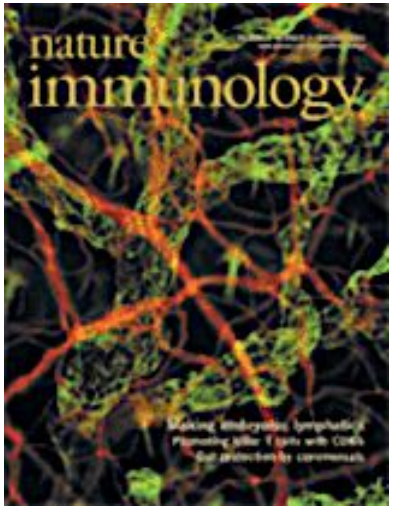

Reference:
Honkonen et al,
Ann. Surg. 257(5): 961-7, 2013

# Strong science:
## from VEGF-C discovery to adenoviral VEGF-C gene therapy




Vol 15, Issue 2, 15 Jan 1996;
Joukov et al
**A novel vascular endothelial growth factor, VEGF-C, is a ligand for the Flt4 (VEGFR-3) and KDR /VEGF-2) receptor tyrosine kinases**


Vol 276, Issue 5317, 30 May 1997;
Jeltsch et al
**Hyperplasia of lymphatic vessels in VEGF-C transgenic mice**




Vol 5, Issue 1, Jan 2004;
Karkkainen et al
**Vascular endothelial growth factor C is required for sprouting of the first lymphatic vessels from embryonic veins**


Vol 18, Issue 14, Nov 2004;
Saaristo et al
**Adenoviral VEGF-C and VEGF-C 156S restore drainage of lymphatic fluid across the incision wound**

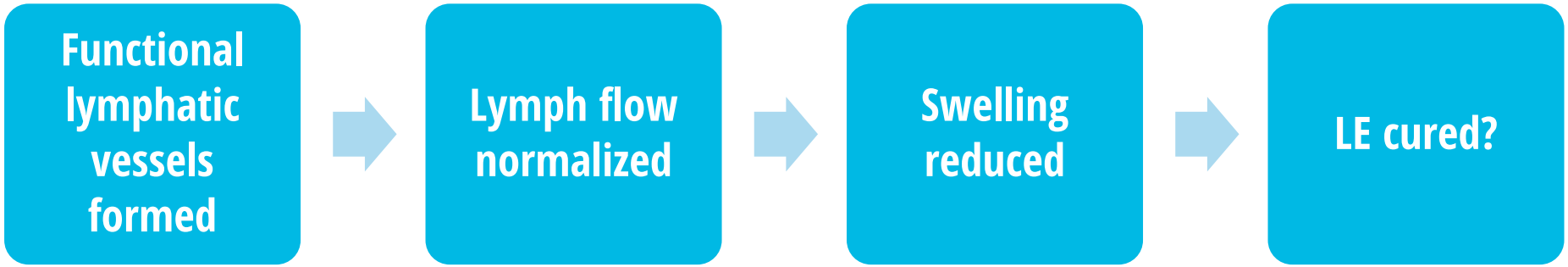
# Academy professor Kari Alitalo
## is the inventor of Lymfactin®

- Director of Translational Cancer Biology Research program, University of Helsinki
  - **National Center of Excellence**
- Internationally leading expert in endothelial growth factors in cancer
  - More than **500 peer-reviewed scientific publications** in biomedicine, cancer research, and cell and molecular biology
  - Receiver of numerous international science prizes including InBev-Baillet Latour International Health Prize, Louis Jeantet Prize for Medicine, Anders Jahre Prize, Dr. A.H.Heineken Prize
  - Foreign associated member of the **National Academy of Sciences of the USA**
- **VEGF-C growth factor** was discovered by Prof. Alitalo, member of Herantis' advisory board

# Development of Lymfactin® into a therapeutic available for LE patients

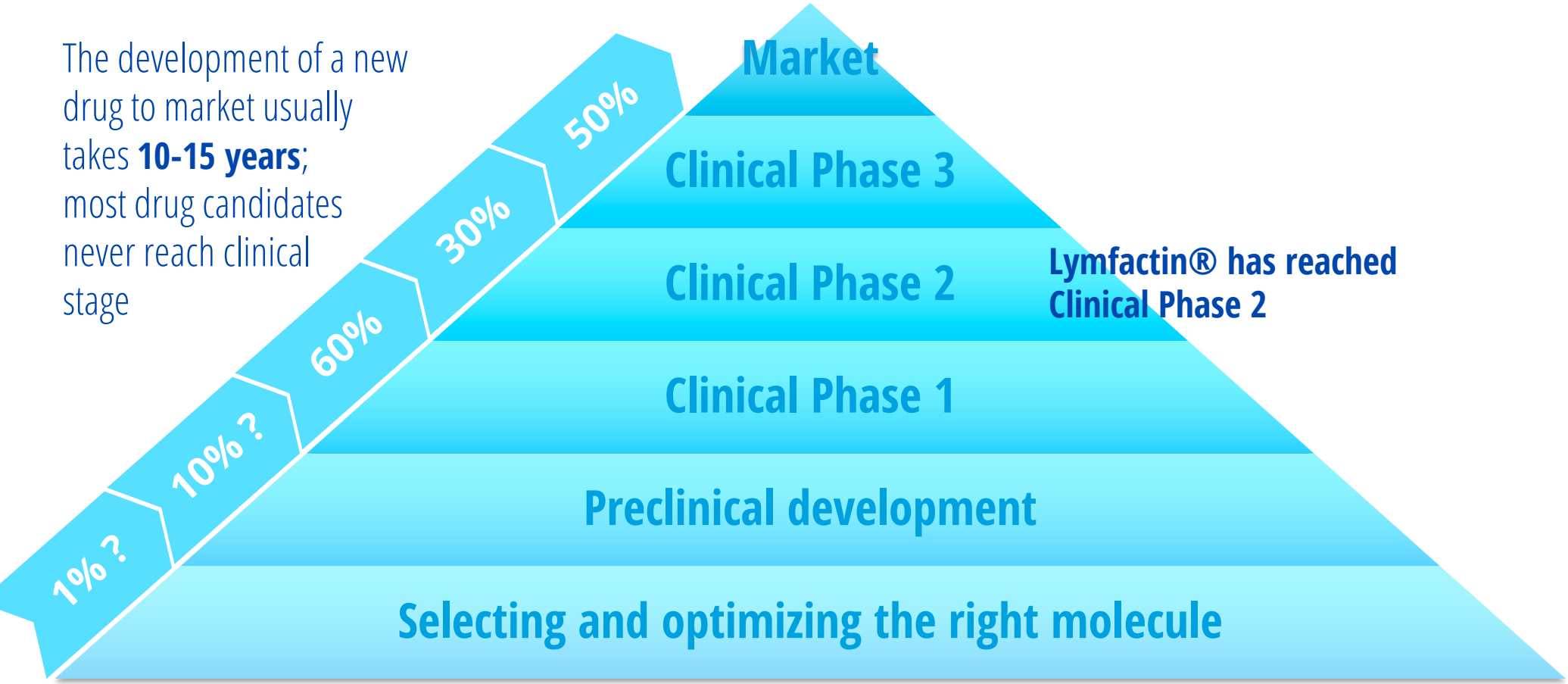
# So what good will that science do in practice?

Lymfactin® is currently in formal clinical development. **If** it works as well in humans as it does in the disease models:



# Drug development is slow and regulated

The development of a new drug to market usually takes **10-15 years**; most drug candidates never reach clinical stage

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# Lymfactin® in clinical development

- Development of new drugs is very slow: Patient safety is always the #1 priority, and therefore years of preclinical studies are required before clinical studies
  - This is already **completed for Lymfactin®**
- As the next step, clinical safety is assessed in a Phase 1 clinical study
  - This is already **completed for Lymfactin®, in real LE patients**
- Efficacy is assessed in Phase 2 clinical studies, usually in a well-defined patient population
  - We have **today launched Phase 2 study AdeLE** in patients with breast cancer associated LE
  - The patients are undergoing lymph node transfer surgery as LE treatment; in this study, a single dose of Lymfactin® is administered as adjunct to surgery

# Lymfactin® interim Phase 1 results

- Positive interim Phase 1 data on Lymfactin® were announced by Herantis in April 2018, in patients with **breast cancer associated secondary lymphedema (BCAL)** in combination with lymph node transfer
- Based on data from 15 patients with BCAL: Lymfactin® is safe and well tolerate
- Promising quality-of-life changes observed; however those are uncontrolled data

# Phase 2 study AdeLE launched in 1H/2018

- **AdeLE**: Adenoviral gene therapy for the treatment of LE
- Randomized, **placebo-controlled**, double-blinded Phase 2 clinical study in patients with BCAL
  - Total of 40 patients will be randomized 20+20
  - Patients will be recruited at 5 - 6 clinical sites in Finland and Sweden
  - Lymph node transplantation + Lymfactin® vs. Lymph node transplantation + placebo
- Single dose Lymfactin® is administered ex vivo in the transplant
- Efficacy will be assessed by several endpoints
  - QoL, volumetric measurements, lymphoscintigraphy, MRI, and LymphScanner™
- The study is expected to be fully recruited by end of 2019
- Unblinding and efficacy read-out will be available after 12-month follow-up

# Key Opinion Leader (KOL) reflections on Lymfactin® as a novel LE therapy

- KOLs are enthusiastic about Lymfactin® being a novel pharmacologic treatment adjunct to surgery with potential **to achieve durable efficacy**
- Delivering VEGF-C with an adenovirus to durably treat underlying pathology is highly attractive
- BCAL as the most prevalent cancer-related secondary lymphedema is considered a relevant starting primary indication for Lymfactin®
- Quality of Life measures are considered very important in clinical development

# Lymfactin® as standalone therapy, and in other lymphedemas?

- In addition to the ongoing Phase 2 study in BCAL, Herantis is considering another Phase 2: Lymfactin® as **standalone therapy** in any secondary LE
  - Possible design of the clinical study: Lymfactin® administration in patients with secondary LE, after removal of scar tissue
  - Scientific rationale: Based on published scientific data Lymfactin® triggers the growth of new lymphatic vessels across incision wounds

# Summary on Lymfactin®

# Lymfactin® aims at curing secondary lymphedema

- Lymfactin® is the world's first and only clinical stage gene therapy that **repairs damages of the lymphatic system**
- Currently in Phase 2 clinical study **AdeLE** in Breast Cancer Associated LE (BCAL) in Europe; initial safety has already been established in a Phase 1 clinical study
- Lymfactin® is based on the internationally leading scientific research by professor Alitalo, foreign member of the **US National Academy of Sciences**
- More information:
  - Herantis' Lymfactin® website: http://herantis.com/pipeline/lymfactin-for-lymphedema/
  - Introductory video on Lymfactin®: https://youtu.be/pJ-m9k3G38Q

# Thank you

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