CDNF: Novel neuroprotective and neurotrophic factor for disease-modifying treatment of Parkinson’s disease, ALS, and other neurodegenerative diseases

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Pekka Simula, CEO
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Herantis Pharma Plc

- Drug development company developing novel pharmaceutical products based on leading science

- Focus in regenerative medicine

- Expertise in early clinical development
  - Preclinical research
  - Early clinical research
  - Clinical Proof-of-Concept

- IPO in Finland June 2014 raised approximately 20 MUSD
# Herantis portfolio (drug candidates)

<table>
<thead>
<tr>
<th>Drug candidate</th>
<th>Indication</th>
<th>Preclin</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
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<tbody>
<tr>
<td>CDNF neuroprotective factor</td>
<td>Parkinson’s disease</td>
<td></td>
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<tr>
<td>CDNF neuroprotective factor</td>
<td>Amyotrophic lateral sclerosis (ALS)</td>
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<tr>
<td>CDNF neuroprotective factor</td>
<td>Alzheimer’s disease</td>
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<tr>
<td>Lymfactin®</td>
<td>Secondary lymphedema</td>
<td></td>
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<tr>
<td>Cis-UCA Eye Drops</td>
<td>Dry Eye</td>
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<tr>
<td>Cis-UCA Emulsion Cream</td>
<td>Atopic dermatitis</td>
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*This stage of clinical development in planning and scheduled
**Active development currently not on-going. Next steps are pending later decisions.
CDNF for Parkinson’s disease (PD)

Based on preclinical data we believe that CDNF is the most promising new compound for a disease-modifying treatment of Parkinson’s disease.

- Parkinson’s disease is an incurable, progressive neurodegenerative disease
  - Estimated seven million patients worldwide
  - Available treatments only help motor symptoms of the disease

- CDNF aims to relieve both motor and non-motor symptoms and slow down disease progression
  - CDNF protects and restores dopaminergic neurons based on preclinical studies in several Parkinson models
  - Based on preclinical data CDNF is clearly more potent than GDNF, which is finishing Phase 2 and partnered to Pfizer
  - First-in-Human clinical study planned to start patient treatments in 2016: N=18, randomized, placebo-controlled
CDNF (Cerebral Dopamine Neurotrophic Factor)

- **CDNF** (a.k.a. rhCDNF) is a novel ER stress-protective factor (Lindholm et al, Nature 448: 73-77, 2007)
  - **CDNF is not another GDNF**
  - Found in normal human plasma and CSF
  - **CDNF has been described as injured cell or ER stress-specific neurotrophic factor, which leaves healthy neurons unaffected (more benign expected safety profile)**
  - **CDNF is expressed in the brain including the midbrain and in several non-neuronal tissues**
  - The neuronal phenotype of CDNF knockout mice supports a significant dopaminergic function*

- **CDNF** protects neurons and restores their functional activity in multiple preclinical models of PD, ALS, and other non-disclosed neurodegenerative conditions
  - Clearly more potent when compared to competitors such as GDNF

- **CDNF** has a distinct mechanism of action
  - Effectively protects and promotes repair of stressed cells
  - Prevents cell death

- **Herantis** develops CDNF in close collaboration with professor Mart Saarma, ERC Vice President and leading expert in neurotrophic factors

* Unpublished data
## Comparison of CDNF with...

<table>
<thead>
<tr>
<th>Nature of polypeptide</th>
<th>CDNF</th>
<th>GDNF&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Neurturin&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>preCDNF</td>
<td>preproGDNF</td>
<td>preproNRTN</td>
</tr>
<tr>
<td></td>
<td>Monomer (18 kD)</td>
<td>Homodimer (32 kD)</td>
<td>Homodimer (25 kD)</td>
</tr>
<tr>
<td>Binding to heparin and ECM</td>
<td>Low</td>
<td>Strong</td>
<td>Very strong</td>
</tr>
<tr>
<td>Diffusion in rat brain</td>
<td>Good</td>
<td>Limited</td>
<td>Very limited</td>
</tr>
<tr>
<td>Protection of TH+-fibres in 6-OHDA model</td>
<td>Very good</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>Protection of cell bodies in MPTP neurorestoration MPTP model</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Neurorestoration in severe 6-OHDA model with continuous infusion of NTFs</td>
<td>Efficient</td>
<td>Trend</td>
<td>Not available</td>
</tr>
<tr>
<td>Improvement in motor symptoms in rhesus monkey</td>
<td>Very good</td>
<td>Good</td>
<td>Not available</td>
</tr>
<tr>
<td>Improvement in non-motor symptoms in rhesus monkey</td>
<td>Efficient</td>
<td>No</td>
<td>Not available</td>
</tr>
<tr>
<td>Clinical signal of disease modification</td>
<td>Not available</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<sup>1</sup>For details and full literature references please contact Herantis Pharma for a copy of a comparison white paper.

<sup>2</sup>Currently in its fifth clinical study with an improved administration technology. In the previous blinded phase 2 study (Amgen), efficacy signal was seen after exclusion of patients with faulty delivery systems. CDNF has a superior preclinical efficacy profile and much improved diffusion in brain compared to GDNF.

<sup>3</sup>Tested in clinical studies by Ceregene (gene therapy). Though the effect of Neurturin was modest it was one of the first times in the history of chronic neurological disease that neurodegenerative disease progression was slowed down in human patients.
CDNF for ALS (Lou Gehrig’s disease)

ALS is an aggressive motoneuron disease with no cure. In preclinical studies, a single CNDF injection has significantly prolonged survival and reduced symptoms of ALS

- In the golden standard ALS model, a single CDNF dose at symptom onset showed:
  - Significant survival benefit (daily Riluzole started before symptom onset shows mixed results in the same model)
  - Clear improvements in motor coordination, balance, and muscle strength
  - Preservation of motor neurons and neuromuscular junctions
  - Reduction of ER stress

- CDNF was granted Orphan Designation for treatment of ALS in Europe in March 2016
- Preclinical development continues
- Herantis is looking for partners for clinical development program
CDNF for Alzheimer’s disease

Published preclinical evidence suggests Herantis’ CDNF improves long-term memory in a mouse model of Alzheimer’s Disease (AD), with no side effects

- CDNF reduces ER (endoplasmic reticulum) stress, which is linked to AD
- Recent publication in Behavioural Brain Research suggests that in addition to reducing ER stress, CDNF also improves long-term memory in a mouse model of Alzheimer’s disease
  - Further, CDNF even improved long-term memory in healthy mice, compared to vehicle-treated animals

- AD is the most common neurodegenerative disease and the cause in majority of cases of dementia
  - Estimated 20 million AD patients worldwide
  - No cure is known

- Current statistics estimate 75 million dementia patients in 2030
- Herantis is looking for partners to launch a development program in AD
CDNF First-in-Human study: Overview

- Phase I/II, placebo-controlled, randomized, blinded safety study in three European university hospitals with leading PD expertise
  - 18 patients with Parkinson’s disease
  - Intracerebral administration of CDNF or placebo 4-weekly for 6 months, using a medical device similar to Deep Brain Stimulation
  - Extension protocol where all patients receive CDNF for 6 months
  - Advanced exploratory endpoints including PET based analysis
- Study design and protocol finalized based on extensive discussions with authorities

Herantis Pharma summary

• Ongoing clinical development: Two fully funded clinical studies in regenerative medicine
  – CDNF for a disease-modifying treatment of Parkinson’s disease
  – Lymfactin® for the treatment of secondary lymphedema caused by breast cancer treatments

• Actively looking for development partners:
  – Clinical development of CDNF in new indications including ALS, Alzheimer’s Disease, and an undisclosed neurodegenerative disease with strong unpublished preclinical data
  – Cis-UCA Eye Drops for the treatment of Dry Eye, Phase 2 completed
  – Cis-UCA Emulsion Cream for the treatment of skin inflammations
Thank you

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